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# THE JOURNAL OF INDUSTRIAL HYGIENE

## AND ABSTRACT OF THE LITERATURE

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Industrial Dermatoses

Summary of Notes on Two Fatalities Due to Inhaling Phosgene ($COCl_2$)

Observations on the Reliability of the Comf-Thermometer (Fresh-Air Gauge) as an Indicator for the Cooling Effect of Air

The Pharmacology of Some Phenylenediamines
*(Continued)*

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# THE JOURNAL OF INDUSTRIAL HYGIENE

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## INDUSTRIAL DERMATOSES*


H. N. COLE, M.D., AND J. R. DRIVER, M.D.

*From the Department of Dermatology and Syphilology of the Medical Department of Western Reserve University and of the Lakeside and Cleveland City Hospitals*


THE subject of industrial medicine has come to the front more and more during the past few years. This is not without reason when one considers the enormous number of patients suffering from some physical disturbance brought on by their occupation; and in no part of the field is this more commonly noted than in connection with diseases of the skin. According to Knowles industrial dermatoses constitute one-sixth of the total number of diseases of the skin; Hazen gives the figure as one-fifth, Oppenheim as four-eighteenths, and Prosser White (1) as one-fourth. In a recent lecture before the Harvard Medical School, White (2) spoke of at least forty-six different diseases of the skin that are well known among approximately 120 different occupations; and Ormsby (3), after inspecting several plants where binding twine is manufactured, found that about 25 per cent. of the workmen were affected with dermatoses due to their occupation. In fact, an investigation of industrial establishments in general would reveal an astounding amount of occupational skin disease.

Since skin affections are so common, it will be of value to us to look, for a moment, into the subject of their etiology. Many different classifications have been used in considering these affections, but we know of none that is any simpler or any more comprehensive than that suggested by Pusey, who groups these diseases according to their predisposing causes and their exciting causes.

There is no question that personal susceptibility has something to do with the dermatitides seen in persons carrying on certain types of occupations. Why one gardener is poisoned by the primrose and another is not; or why one person has a dermatitis from working with rosewood, while another person has no ill effects, is difficult to explain. To a large extent we must explain it as a case of personal susceptibility or, perhaps, a type of anaphylaxis. It is certainly true


*Read at the joint meeting of the Industrial Hygiene Section of the American Public Health Association and the Ohio Association of Industrial Physicians, Oct. 18, 1922. Received for publication Oct. 21, 1922.

that once a person has been poisoned by a particular substance his susceptibility to it is undoubtedly increased. It has been noticed that workers who have once been sensitized to satinwood almost have an anaphylactic shock, not only of the skin but of the entire system, if they even enter the room where this wood is being worked. We have all heard of people who are susceptible to such substances as buckwheat flour. Is not the personal susceptibility of industrial workers much the same?

In addition to personal susceptibility, however, there are certain other predisposing causes which must be mentioned. Why is it that the colored man is so free from industrial dermatoses, in comparison with the white man? Is it due to the fact that his skin is more oily, and consequently gives him better protection? This is undoubtedly true, and it may also explain, to a certain extent, why the person with a dry skin is so much more susceptible to industrial dermatoses than is the person with an oily skin. The brunette, whose skin approaches more nearly that of the negro, is probably less susceptible than the blond. Again we find that in certain industries the old person or the person with the senile type of skin suffers more from skin affections than does the youthful person. This is probably due to lack of oil in the skin, and we feel quite free in saying that in many instances this predisposing cause, together with personal susceptibility, has a great deal to do with the dermatoses seen in the average industrial plant.

All dermatoses cannot be explained in this way, however, and other reasons for their presence, such as the exciting causes, must be sought. It is a well-known fact that leprosy is a disease of the tropics, and is exceedingly uncommon in the average locality in the temperate zone. This applies also to a number of other diseases. There is no question that the climate has some effect, especially in producing the dermatoses which are excited in part by excessive perspiration. This brings up the subject of temperature, which is closely allied to climate as an exciting cause. During the war we heard of the trench feet of the soldiers, a disease undoubtedly due to deficient circulation and to the cold. Among men exposed to the heat of a furnace in their daily work, also, there frequently occurs an erythematous dermatitis on the exposed parts of the body.

Mechanical pressure likewise is the cause of many trade skin changes, such as the hygromata of tailors and carpenters, the "beat" knee of the collier, and

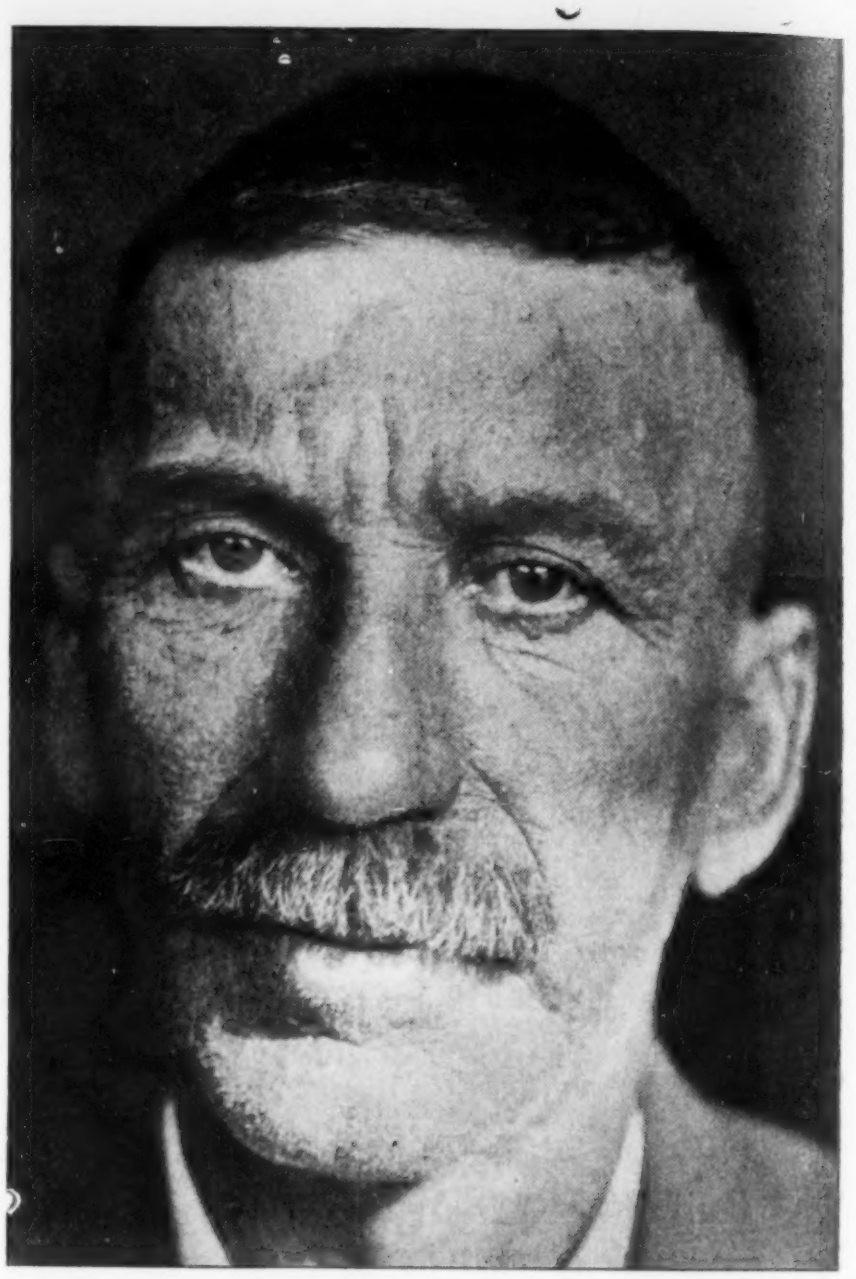

FIG. 1.—Case of hypersusceptibility, in a farmer, to horse dandruff.

the "beat" hand of the miner.

Parasites may also be the exciting cause of puzzling complaints in industrial workers. Legge (4) describes a dermatitis of the hands and exposed parts of the body, gradually spreading

FIG. 2.—Dermatoconiosis, from metallic dust, in a worker engaged in filling boxes with tacks. One week after stopping work, the back was practically well.

over the entire body, seen in packers in some tile plants in California. Careful examination of the straw in which the workmen packed the tile revealed the fact that it was infested with pediculoides ventricosus. Elimination of these organisms from the straw caused the entire disappearance of the dermatoses. Numerous other examples of inflammations of the skin due to parasites might be mentioned.

Again, many of these conditions may be explained from a purely mechanical standpoint. Skin affections of this kind we term dermatoconioses. They are frequent among persons working with powders of different types, especially finely divided powders. As examples, we may cite workers in zinc oxide powders, as in a group recently reported by Turner (5), and workers with pyrethrum, iron ore dust, and copper dust. The particles of powder which are floating about in the air, alight on the skin and clog the pores of the sebaceous and sweat glands. This irritates the skin and then secondary infections set in.

We have recently seen a patient with a generalized follicular eruption on the exposed parts of the body who stated that her sole task was to fill paper boxes with tacks from an automatic machine. She said that there was no oil in her work but that there was a great deal of fine metallic dust flying around and

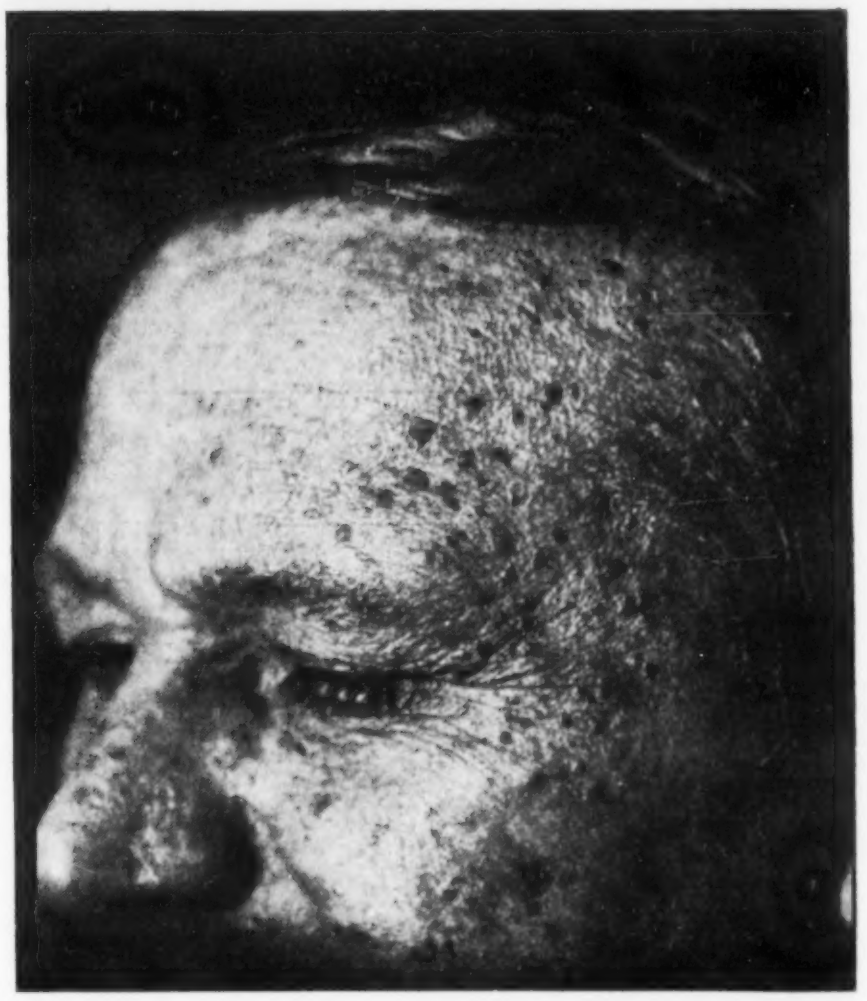

FIG. 3.—Keratoses in a carbon worker. This patient has not worked with carbon for twenty years. Several areas have undergone malignant change.

alighting on her skin. This was clearly a case of dermatoconiosis. Undoubtedly some of the skin affections seen in workers with tar and carbon can be explained in the same way.

During the war many cases of trinitrotoluene dermatitis were observed. The condition was due primarily to the fact that the pores of the skin became clogged with the powder, and secondarily to the fact that the powder

was covered with minute, sharp, spicules which seemed to irritate the skin. This type of dermatitis has been carefully studied and reported on by Prosser White (1) (6) and others. Many of the cutaneous affections seen in candy workers, workers in flour mills, and grocers are of the same etiological group.

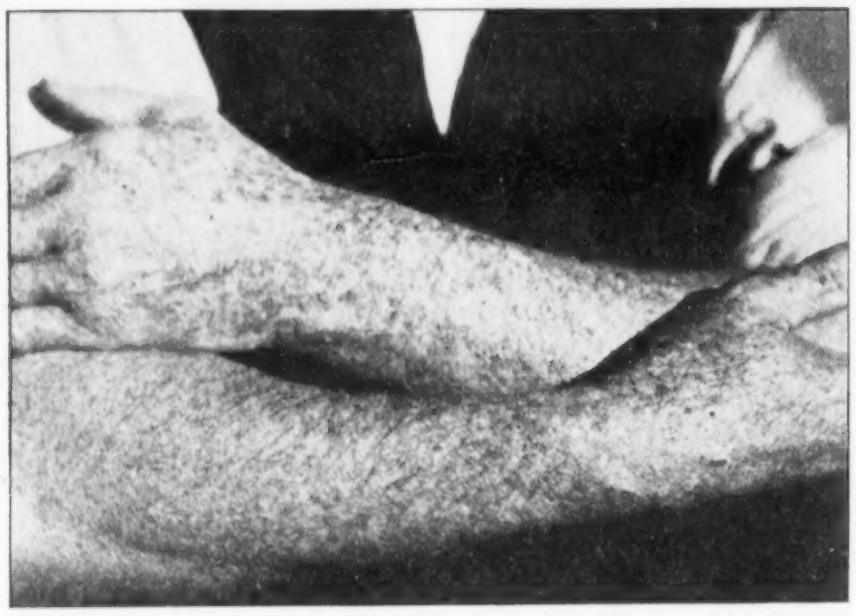

FIG. 4.—Chronic dermatitis in a carbon worker.

There is no class of industrial skin diseases in which the mechanical theory of the exciting cause plays a more important part than in the class of dermatoses resulting from the use of cutting oils. In order to minimize the heat from friction in the use of high speed metal cutting machines in industry various combinations of oils and lubricants have been devised. They contain animal and vegetable oils, free fatty acids, so-called sulphonated oil (which is oil treated with sulphuric acid), etc. As an economic measure it has been the custom in industrial plants to use these oils over and over, with the result that sooner or later the skins of many of the workmen become severely inflamed and infected.

This subject has been carefully studied for many years. One of the best of the early contributions on the subject was by Shie (7). He concluded that the cutting oils used among lathe workers became secondarily infected by repeated use; moreover, the workers expectorated into them, and otherwise contaminated them, so that they became loaded with bacteria which would infect the skin of the workmen, especially if they had any open skin lesions due to flying particles of metal, etc. Shie checked up his work carefully from a bacteriolog-

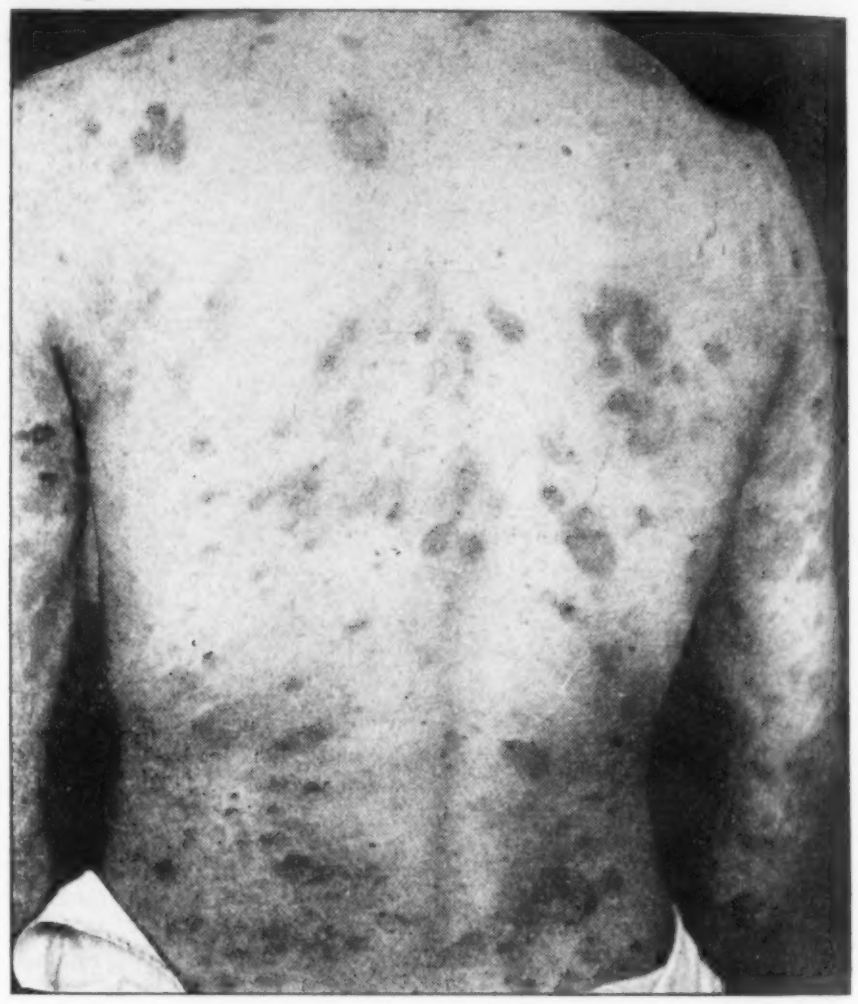

FIG. 5.—Generalized grocer's dermatitis.

ical standpoint. He also found that in the plant which he studied the wounds were reduced from 5 per cent. to less than 0.5 per cent. by treating the oils with a combination of heat and chemical disinfectant. His findings have been reviewed by the Houghton Research Staff (8) and by Page and Bushnell (9). McLachlan (10) has recently published an independent study on the same subject, in which he corroborates Shie's findings, and in addition lays stress on the presence of free fatty acids in the cutting oils, and on personal and occupational hygiene.

Perhaps the recent investigation of McConnell (11) is the best that has thus

far been made. Under the auspices of the United States Public Health Service he made a study of the larger plants in Chicago, Minneapolis, and St. Paul, in order to ascertain the exact causes of the dermatoses due to the use of oils and lubricating compounds. In his investigation he found that among 2,060 workers 27 per cent. had a dermatitis characteristic of this type of work. The most frequent symptom was the presence of an affection known as "oil acne," appearing primarily as comedones at the orifices of the hair follicles and seen especially on the exposed parts of the body and over the thighs where the oil from saturated clothing comes into intimate contact with the skin. This eruption is usually accompanied by severe itching, and there may be secondary infections resulting in large furuncles and abscesses. As a result of his investigation McConnell came to the conclusion that while it was true that infection might have something to do with these dermatoses; that while it was true that the free fatty acid and free sulphuric acid present in the cutting oils and lubricants might irritate the skin to a certain extent; and that while it was also true that the pickling compounds present on the metals to be worked might irritate the skin of the workmen; yet, in his estimation, the mechanical theory alone was sufficient to explain the presence of most of the lesions. He found that the affection was more frequent in persons with dry skins, and that in these persons it was caused by the mechanical obstruction of the sebaceous ducts. These findings apply likewise to his report on the dermatoses found among printers (12).

FIG. 6.—Dermatitis of the hands in a candy worker.

FIG. 7.—Oil dermatitis of the hand. Patient works at an oil tempering bath.

It is true that many of the industrial dermatoses can be explained from the mechanical standpoint, yet many of them must be considered from the chemical standpoint as well. As instances, may be cited the dermatoses among workers with lacquer, which is made from Japanese and Chinese rhus; among leather workers, who come into contact with arsenic, hydrochloric acid and potassium dichromate; among painters using methyl alcohol, with its poisonous

er as he enters the workshop, to insure the efficient carrying out of the foregoing.

4. At noon, before eating luncheon, the workmen should wash the hands and forearms with warm water and soap.

5. On returning to work they should repeat the morning schedule of washing and applying the lanolin preparation.

6. At the end of the workday they should wash the hands and arms with warm water and soap and dry them. No emollients should be applied unless actual abrasions are present, in which event proper dressings should be applied. The lesions on the thighs can best be prevented by wearing aprons impenetrable to oils.

In plants inspected by McConnell and in which his instructions were enforced, after eight months no industrial dermatoses were found; while in plants where the routine measures were adopted but were not enforced, 21 per cent. of the men still had dermatoses. This shows the efficacy of these recommendations. In concluding, we wish to emphasize the importance of cleanliness in the hygiene of industrial dermatoses.

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# SUMMARY OF NOTES ON TWO FATALITIES DUE TO INHALING PHOSGENE ($COCL_2$)*

THE LATE SHERIDAN DELÉPINE, M.B., C.M., M.Sc.

THE two men whose cases are here reported were employed during the war in factories where they were exposed to the risk of inhaling phosgene.

CASE 1.—X was seen by the works physician on March 27 at 3:15 P.M.; after that he went to work but returned very soon, obviously suffering from gas poisoning, and with his clothing saturated with phosgene. He was treated immediately and was attended until 5 P.M.; his pulse was then good, and, as he was much better, he was sent home. At 9:30 P.M. he became worse. He was deeply cyanosed, his respiration was difficult and rapid, and there was frequent coughing and expectoration of a large quantity of frothy mucus. Under treatment he improved and was distinctly better at 1:30 A.M. He had a relapse at 9:30 A.M. on March 28, and he died at 11:15 A.M.

From this brief history it appears that X was well and able to work at 3:15 P.M. on March 27, and that he was gassed about 4 P.M. and died nineteen hours later.

CASE 2.—As the result of the explosion of a cylinder containing phosgene gas, which took place at 3:30 P.M. on June 11, Y was exposed to the action of the gas and one of his hands had to be amputated at the wrist. There was little hemorrhage, either before, during or after the operation, and at the end of the operation the patient appeared to be comfortable. The breathing became distressed and the pulse rapid at about 10 P.M., and death occurred at 1:30 P.M. on June 12, twenty-two hours after the accident.

The various organs of the body in both cases were submitted for examination; the findings are summarized in Table 1.

## REMARKS

The lesions observed in the two cases reported fall under three categories: (1) Pre-existing lesions (*i.e.*, lesions not attributable to phosgene poisoning); (2) primary lesions due to inhalation of phosgene; and (3) secondary lesions, which may be considered as the physiological consequences of the primary lesions.

### *Pre-Existing Lesions*

*Heart.*—In both cases (and more particularly in the case of Y) the heart was larger and heavier than the normal average, and its cavities were slightly dilated. There was, however, no chronic cardiac or extra-cardiac lesion that could account for any degree of hypertrophy or dilatation of the heart, except the limited fibrosis of the apices of the lungs in one case. As the body weight of the men is not known, no inference can be drawn from the heart weight.

*Lungs.*—In the case of X the apices of both lungs were in a state of fibrosis (fibroid pneumonia), which was probably due to healed tuberculosis; the amount of lung tissue thrown out of use

*This article was kindly placed at the disposal of THIS JOURNAL by the author's literary editor.
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pyridine; and among paper-hangers who come into contact with aniline dyes. In this section of the United States we see many employees of rubber plants working with such poisonous aniline derivatives as para-phenylenediamine and thiocarbanilide, and with formic acid and formaldehyde, decomposition products of hexamethylenetetramine. In these industries the dermatoses are due partly, at least, to the action of the chemical irritant. Personal susceptibility may, however, be a contributory cause. Among nurses and physicians there occur numerous instances of still another type of chemical irritation, in which, also, personal susceptibility plays a part. We refer to the erythematous dermatoses seen so frequently on the hands of nurses and physicians as a result of using bichloride of mercury, iodine, and various chlorine preparations.

McConnell and others have found that in many instances there is still another thing to be considered as an etiological factor in industrial dermatoses—namely, the fact that often workers use such strong soaps and such harsh stiff brushes to remove the oils, dyes, metallic dust, etc., that they injure their skins.

No paper on industrial dermatoses today would be complete unless it included reference to the dermatitis seen in physicians and X-ray workers. Despite a great deal of educational propaganda we still see X-ray equipments installed with inadequate facilities for the protection of the operator. Probably in the next few years we shall see even more damage done by radium. The writers are personally acquainted with several physicians and radium workers who have been irreparably injured by exposure to these elements. We believe that there should be stringent laws for the protection of workers with X-rays, especially, and also, if possible, for the protection of workers with radium.

Finally, there is still one other group of causative factors in connection with industrial dermatoses—namely, the bacterial group. As examples of skin diseases of bacterial origin we may mention anthrax, which occurs among workers with leather and with brushes, and mycotic diseases, such as blastomycosis and sporotrichosis, which are fairly common in the meat packing industry.

In fact, if we look over the entire subject of industrial medicine, we find that industrial dermatoses and their causes are innumerable. The symptoms are likewise numerous, though as a rule they are not so numerous that they cannot be quite readily diagnosed. The patient generally gives a history of their acute onset, especially of their appearance soon after he has started a certain occupation, but not infrequently of their appearance after he has worked at the same occupation for some time. Why a man can work with a certain type of wood, for example, for several months without displaying any symptoms, and then suddenly show symptoms of acute poisoning of the skin, is difficult to explain. Nevertheless, instances of this type are not uncommon.

The lesions of industrial dermatoses are usually sharply limited to the exposed parts of the body, and this fact is of assistance in the diagnosis. Sometimes in persons having the condition for a long time, however, the lesions may become more generally distributed. In persons working with oils, the trousers, especially over the thighs, may become saturated with the oils, and a dermatitis of this area as well may result. In persons working with powders such as lamp black, or in chimney-sweeps,

the powder may get into the clothing as well as on the exposed parts of the body, and may bring about some generalized type of dermatitis. As a rule, however, the process is localized on the exposed parts, and this should suggest the possibility of an external irritant as the source of the affection. It is seldom that other conditions have to be considered. Occasionally one will see a frequently recurring eruption sharply limited to one limb, in an area easy to reach, which may be diagnosed as dermatitis factitia. Some time ago we saw such a case. The patient had an indolent ulcer on one forearm which had lasted for years and had cost her firm thousands of dollars. She was accustomed to keep it open by the application of a little phenol from time to time. Fortunately, this type is rare. Occasionally a seborrheic dermatitis may be brought into the question, but it is rare for a seborrheic dermatitis to be limited to the exposed parts, and especially for it to come on so acutely and without the symptoms involving the scalp.

Once a diagnosis has been made, the question of treatment arises. Here several things should be considered. In the first place, the cause should be ascertained and, if possible, should be removed. It will probably be necessary to transfer the workman affected to another part of the plant, or perhaps to give him a short rest. The treatment of the condition, however, will be one of the simpler things to be considered, and should consist in local application of non-irritating, soothing remedies. As a rule ointments are contraindicated, particularly in the acute stage. Rather the use of lotions or hot soaks—perhaps of potassium permanganate in water, 1:5,000—is recommended; or the use of 1 per cent. aluminum acetate in distilled water. Boils and abscesses should be treated according to the surgical indication. After the acute symptoms have subsided, it may be justifiable to use a mild, soothing ointment, such as 5 per cent. boric acid ointment. Many times in thickened areas of chronic inflammation we find the local use of the X-ray in unscreened doses of approximately one-half skin unit to be of great value. In colored people, because of their tendency to keloids, we advise the prophylactic use of one or two X-ray treatments after lacerations.

The hygiene of industrial dermatoses is the point on which we should lay the greatest stress, as prevention of the condition is much easier than its cure. We believe that there is not close enough supervision of industrial workers. Shower baths should be available in all industrial plants, and it should be compulsory for workmen to use them daily—certainly, after finishing their work at night. They should not be allowed to wear clothing saturated with oils or filled with powders which have the capacity to cause chemical or mechanical injury to the skin. Fresh clothing and frequent bathing will prevent most industrial dermatoses. On the other hand, workmen must not overdo bathing to the extent of injuring the skin.

The prophylactic measures suggested by McConnell seem to us so important that we are giving them in full.

1. On entering the plant each workman should wash the hands and forearms thoroughly with warm water, using a sawdust and liquid-soap preparation to assist the cleansing process.
2. After drying the skin with an individual towel he should apply either lanolin alone or lanolin and castor oil, and rub it well into the skin.
3. The foreman should inspect each work-

er as he enters the workshop, to insure the efficient carrying out of the foregoing.

4. At noon, before eating luncheon, the workmen should wash the hands and forearms with warm water and soap.

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The various organs of the body in both cases were submitted for examination; the findings are summarized in Table 1.

## REMARKS

The lesions observed in the two cases reported fall under three categories: (1) Pre-existing lesions (*i.e.*, lesions not attributable to phosgene poisoning); (2) primary lesions due to inhalation of phosgene; and (3) secondary lesions, which may be considered as the physiological consequences of the primary lesions.

### *Pre-Existing Lesions*

*Heart.*—In both cases (and more particularly in the case of Y) the heart was larger and heavier than the normal average, and its cavities were slightly dilated. There was, however, no chronic cardiac or extra-cardiac lesion that could account for any degree of hypertrophy or dilatation of the heart, except the limited fibrosis of the apices of the lungs in one case. As the body weight of the men is not known, no inference can be drawn from the heart weight.

*Lungs.*—In the case of X the apices of both lungs were in a state of fibrosis (fibroid pneumonia), which was probably due to healed tuberculosis; the amount of lung tissue thrown out of use

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TABLE 1.—SUMMARY OF LESIONS FOUND IN TWO CASES OF PHOSGENE POISONING

| Organ or Material | X (Lesions 48 Hrs. after Death) | Y (Lesions 31 Hrs. after Death) |
|---|---|---|
| *Heart* | | |
| Without blood | 295 gm., large, flabby, semi-contracted. | 340 gm., flabby, semi-contracted. |
| Blood | 170 gm., soft homogeneous clot; normal. Color brightening on exposure to air. | 170 gm., homogeneous clot. Venous looking, brightening rapidly on exposure to air. |
| Pericardium | Normal. | Normal. |
| Epicardium | Normal. | Milk spots near apex of left ventricle. |
| Endocardium and valves | Normal; blood stained. | Normal. |
| Myocardium | Granular degeneration (incipient necrosis?); congestion. | Granular degeneration; slight congestion. |
| *Aorta* | | |
| First part | Limited soft atheroma. | Limited soft atheroma. |
| *Lungs* | | |
| With exudate in bronchi | 1,559 gm. | 1,340 to 1,350 gm. |
| After escape of exudation | 1,460 gm.: right, 750 gm.; left, 710 gm. Lungs remain distended with air, as in inspiration. | 1,190 gm.: right, 644 gm.; left, 546 gm. Lungs remain distended with air, as in inspiration. |
| Pleura | Old fibrous adhesions at apices of both lungs. Subpleural emphysema. | A few loose fibrous adhesions on outer aspect of left lung. Thin deposit or precipitate on serous surface. Petechial subpleural hemorrhages. Subpleural emphysema. |
| Parenchyma | Fibroid pneumonia of both apices. General congestion. Small hemorrhages at basis of right lung. Disseminated alveolar edema alternating with alveolar (vesicular) emphysema. | General congestion; color bright red. Disseminated alveolar edema alternating with alveolar (vesicular) emphysema. |
| Interlobular tissue | Interstitial (interlobular) emphysema. | Interstitial (interlobular) emphysema. |
| Air passages | Capillary bronchitis (and obstruction of terminal bronchi, under 1 mm. only). Acute catarrhal (desquamative) bronchitis, tracheitis, and laryngitis, characterized by extensive desquamation and bronchorrhea. | Capillary bronchitis (and obstruction of terminal bronchi under 1 mm.). Acute catarrhal (desquamative) bronchitis, tracheitis, and laryngitis, edema glottitis and edema of bronchial mucosa. Acute bronchorrhea. |
| *Liver* | Total weight 1,326 gm. Small, normal in shape; generally pale owing to pale color of portal zone of lobules. | Total weight 1,601.7 gm. Normal in shape; generally purplish red in color; central parts of lobules congested. |
| Capsule and interlobular tissue | Normal, irregularly congested. | General slight increase (incipient cirrhosis). |
| Portal vein and branches | Distended with blood; normal in appearance. | Distended with blood; normal in appearance. |

TABLE 1 (*Continued*)

| Organ or Material | X (Lesions 48 Hrs. after Death) | Y (Lesions 31 Hrs. after Death) |
|---|---|---|
| *Liver* (cont.) | | |
| Hepatic vein and branches | Distended with blood: normal in appearance. | Distended with blood: normal in appearance. |
| Parenchyma | Hepatic cells, small, granular, pigmented; evidence of very early stage of fatty degeneration. No distinct necrosis. No deposit of "free iron." | Hepatic cells, small, granular, slightly pigmented; doubtful evidence of early fatty degeneration. No distinct necrosis. No deposit of "free iron." |
| Bile duct and gallbladder | Apparently normal. Moderately filled with dark brown, thick bile. | Apparently normal, except a few of the terminal ducts, which are increased in length (effect of cirrhosis). Moderately distended with dark, greenish brown bile. |
| *Kidneys* | | |
| Right | 115 gm. | 120.5 gm. |
| Left | 130 gm. | 134.6 gm. |
| Both | 245 gm. | 255.1 gm. |
| | Normal in shape and size; general congestion; small retention cyst under capsule of right. | Normal in shape and size; general congestion, but labyrinth pale. |
| Capsule | Slightly thickened. | Normal. |
| Interstitial tissue | Normal in amount. | Slight increase at places under the capsule. |
| Renal vessels | Congested, especially vasa recta and malpighian tufts. | Congested, especially vasa recta and malpighian tufts. |
| Parenchyma | The epithelium of most of the convoluted and spiral tubules is necrosed. In a few groups of convoluted tubules a slight degree of fatty degeneration is noticeable. The straight and excretory tubes are less affected. No "free iron" in any part of the organ. | The epithelium of most of the convoluted tubules is necrosed. Desquamation in a few small groups, with slight amount of fatty dedegeneration. Collecting tubules less affected. No "free iron" in any part of the organ. |
| *Pelvis, Ureter and Bladder* | Mucous membrane much thickened. | Mucous membrane much congested. |
| *Urine* | Pale greenish yellow, turbid. Sediment abundant; vesical epithelium and red blood corpuscles present. | |
| | Specific gravity 1,020. Reaction acid. Albumin abundant. | |
| *Spleen* | 90 gm. Normal in shape. Evidence of congestion. | 102 gm. Normal in shape; somewhat flabby; somewhat pale. |
| *Stomach* | Congestion of all coats. No obvious histological lesion. | General congestion. |
| *Duodenum* | Same. | Same. |
| *Blood from Pulmonary Vessels* | Oxyhemoglobin spectrum; carboxyhemoglobin, no typical absorption bands observed. Oxyhemoglobin entirely reduced by Stokes' fluid. | |
| *Exudate and Tissue from Lung Parenchyma* | 0.49 per cent. chlorine present. | |

was, however, inconsiderable. The remainder of the lungs was free from chronic lesions. In the case of Y the lungs appeared to be entirely free from chronic lesions. The few loose fibrous pleural adhesions had very little pathological significance. Town anthracosis was well marked, but not excessive.

*Liver.*—In both cases the liver was normal in shape; it was slightly below the average normal weight in the case of X, but this decrease did not appear to be connected with any previous lesion. In the case of Y there was a slight amount of cirrhosis, and this may have accounted for the weight being proportionally greater than in the case of X.

*Kidneys.*—These organs were normal in shape and size; a very slight amount of fibrosis was observable, but there were none of the lesions characteristic of interstitial nephritis.

*Spleen, Stomach, and Small Intestine.*—These organs showed no evidence of pre-existing disease.

### *Primary Lesions Due to Inhalation of Phosgene*

The air passages from the larynx down to the terminal bronchi were the seat of lesions attributable to the action of a powerful irritant. The absence of evidence that any other irritant than phosgene had penetrated the air passages justifies the view that the cause of the lesions was phosgene. The laryngeal, tracheal and bronchial epithelium was more or less completely shed. In the larger air passages the basement membrane was generally quite bare. There were no ulcerative lesions. The few epithelial cells remaining attached to the basement membrane and those which, after separation, had remained mixed with the exudate filling the bronchi, were not in a state of necrosis; some of these cells showed evidence of proliferation. Many of the epithelial cells were in a state of mucous degeneration, and it is probable that this condition and the rapid passage of exudate from the mucosa into the bronchi were instrumental in bringing about extensive and rapid desquamation.

The congestion and edema of the mucosa and submucosa, as well as the excessive excretion of mucus by the tracheal and bronchial mucous glands, may reasonably be attributed to the irritating action of the gas.

The obstruction of the terminal non-alveolated bronchi, measuring less than 1 mm. in diameter, by the desquamated epithelium mixed with variable proportions of exudate appears to have been the main cause of the fatal effects of phosgene inhalation.

The lesions observable in the alveolated portion of the parenchyma were partly primary and partly secondary. The intense congestion of the alveolar capillaries, the alveolar edema and also the edema of the interlobular tissue are attributable to a more or less direct action of the irritant. The epithelial or endothelial lining of the alveoli was comparatively little affected; very few alveoli contained an excessive number of desquamated cells. In a few places, however, some of the cells lining the alveoli had been lifted from their places by the exudation. There was an absence of typical croupous exudation. The mucous membrane of the air passages down to the terminal non-alveolated bronchi apparently were more severely affected by the action of the phosgene than were the alveolated passages and the alveoli. This difference can be accounted for on the supposition that the amount of phosgene present in the tidal

air was reduced by dilution with the residual air contained in the alveolated part of the lobules, and probably also by the absorption of a part of the phosgene by the bronchial mucous membrane. The low diffusibility of the gas may also have retarded its penetration.

*Secondary Lesions*

The other lesions found in the lungs and those found in other viscera appear to be secondary to the obstruction of the terminal bronchi.

The most important secondary lesion observed in the lung parenchyma was emphysema, affecting both the alveoli and the interstitial (including the subpleural) tissue. This emphysema was recognizable in every part of the lungs in both cases, except at the apices of the lungs in the case of X. In a certain proportion of the lobules, which were partly edematous, the distention of the alveoli was not so well marked as in the other lobules in which the amount of exudation was less. In most of the lobules the alveolated air passages were free from exudation and distended with air.

Collapse and consolidation of small areas of lung tissues were very limited in extent. Emphysema in the present cases cannot, therefore, be described as due to the compensatory dilatation which is so common a feature in subacute or chronic bronchopneumonia.

The distention of the alveoli appears to have been due to the mechanical effects of an accumulation of air in the lobules. This was complicated by a passage of the air into the interlobular tissue, the subpleural cavity and, in one case, the pleural cavity itself.

These emphysematous lesions were probably brought about by excessive inspiratory movements combined with gradual blocking of the bronchioles. At first the obstruction of the bronchioles was not complete enough to prevent the passage of some air into the lobules; interference with the normal gaseous exchanges induced increased inspiratory movements which, by reducing the pressure of the air in the partly blocked lobules, caused some of the air in the bronchi to bubble through the material blocking the bronchioles. On the other hand, the elasticity of the lung tissue and the expiratory movements were probably insufficient to overcome the resistance offered to the escape of air imprisoned by the bronchial plugs. It is probable that after a short time the terminal bronchi were so firmly plugged that the passage of air became impossible both during inspiration and during expiration.

The lung, at that stage, was comparable to a mass of small closed air balloons with thin walls partly stretched. The effect of excessive inspiratory movements of the chest wall was to reduce the external pressure sufficiently to cause the rupture of the balloons situated near the surface and more particularly at the thin edges of the lungs, where the effects of expansion of the thoracic cavity could not be distributed among a number of lobules as in the more central parts of the organ.

The rupture of some alveoli was followed by the passage of air into the interstitial tissue, and in one case the serous layer of the pleura gave way and air escaped into the pleural cavity, which was found postmortem to be filled with frothy exudate.

According to this view the emphysema observed in cases of phosgene poisoning is an acute mechanical emphysema caused by the obstruction of

terminal bronchi, to which it is secondary.

This explanation appears to be supported by the symptoms which I experienced after a partly accidental, partly voluntary exposure to phosgene.

On February 2, 1917, I had to conduct some tests at the Army Medical College in London. The room in which these tests were made was partly underground, and was ventilated by an opening near the ceiling and by a door opening upon a passage with windows opening upon a small inner court. At the level of the upper opening an experimental discharge of phosgene was made soon after the beginning of my experiments. Two of the gentlemen who were present were obliged to retire very rapidly. My assistant had a gas mask, but in order to see my recording instruments I was unable to wear a mask.

I came into the room at frequent intervals in the course of three-quarters of an hour, in order to take my readings of the instruments. Beyond some irritation of the conjunctivae and of the larynx I was not much inconvenienced at first, but as the amount of gas increased I found it necessary to hold my breath, and not to remain in the room for more than one minute at a time. Toward the end of the experiment the passage to which I retired between the observations was invaded by the gas, which I was obliged to breathe freely. This brought about a violent fit of incoercible coughing, which forced me to inhale a fairly large amount of poisoned air. A medical colleague who was also watching the experiment from the passage was affected in the same way. We both had to run away; but during the flight we had to stop frequently owing to the violence of our cough. Even when we had reached a portion of the building where other people were not inconvenienced by the gas, we continued to cough so violently that our congested faces were running with perspiration. This lasted, as near as I can remember, for about fifteen or twenty minutes; the cough then became more bearable, and we were able to move about. I felt dazed and weak, and even after getting out into the open air it seemed to me that the air was still heavily laden with phosgene. I continued to improve for another three or four hours; then I began to experience a choking sensation, which I tried at first to relieve by breathing deeply. I found, however, that this made me cough again. After a short time I found it best to expand my chest, and to breathe very rapidly (about forty to sixty respirations per minute). This did not, however, relieve the choking feeling which at times gave me a considerable amount of anxiety. I remained panting in this way the greater part of the night. The same feeling recurred several times during the following day and night; after that my breathing became normal, but for several days I suffered from marked lassitude.

Except during the initial period, the cough was not very troublesome. (From what I heard afterwards my colleague was more seriously affected than I.)

I was too ill during the first night to make careful observations, but the sensation of impending death from want of air has remained engraved on my mind. I was not troubled with much expectoration.

These symptoms seem to have been due to spasm of the small bronchi, and the condition was one which had many of the clinical features of asthma. The smell of phosgene persisted for many hours, as did also a peculiar sensation of irritation in the larynx and trachea. The persistence of the smell seems to indicate that some combination takes place between the gas, or some constituent of it, and the superficial layers of the mucous membrane.

The direct action of the phosgene upon the bronchial epithelium does not seem to have produced actual necrosis of the cells, which had remained *in situ*. The staining reactions of the desquamated cells did not resemble those of cells which had undergone necrobiosis or coagulative necrosis. This finding does not in itself prove that these cells had not been rapidly killed before or after being shed.

The fact that many of them showed evidence of mucous degeneration, however, supports the view that the gas acted as an irritant and not as an agent immediately lethal.

The amount of chlorine found in the lung tissue, including the blood contained in the vessels and the exudation in the medium sized and small bronchi, amounted to 4.9 parts per 1,000 parts of the material examined. No

evidence could be found of the presence of an appreciable amount of carbon monoxide in the pulmonary blood. No methemoglobin was revealed by the spectroscope. These results must be accepted with caution, and should be controlled by carefully conducted experiments on animals, before any hypothesis is based upon them.

The lesions observed in the kidneys, liver, and heart all appeared to be secondary to the state of the lungs caused by the obstruction of the terminal bronchi, and were attributable to interference with the gaseous exchanges in the lungs, and the consequent changes in the circulating blood. The gradual but rapid diminution in the amount of oxygen was probably of paramount importance in connection with the production of necrotic lesions.

The renal epithelium in the convoluted and spiral tubules had suffered most severely. The few renal cells which had survived showed evidence of granular degeneration and early fatty degeneration.

The hepatic cells were less affected but were generally in a state of granular degeneration, with a tendency to fatty degeneration. They were not swollen; on the contrary, many of the cells, particularly in the hepatic zone, were shrunken.

The myocardial cells were in a state resembling that of the hepatic cells. The congestion of all the organs was of the mechanical or passive type, being due to obstruction of the pulmonary circulation caused by the emphysematous state of the lungs.

A remarkable feature of most of the lesions which have been described is the rapidity with which they occurred. X died nineteen hours after exposure to the gas, and Y twenty-two hours after exposure.

## Therapeutical Measures Indicated by Pathological Findings

It would appear that as phosgene or the products of its decomposition (probably hydrochloric acid and carbon dioxide) come into contact with the mucous membrane of the larynx, trachea and bronchi, some of the hydrochloric acid is absorbed by the superficial cells, and acts as an irritant. It would, therefore, seem desirable to neutralize any free or partly combined hydrochloric acid in order to limit this irritating action. Neutralization might be effected if an amount of ammonia insufficient to cause marked irritation were contained in the air breathed by the patient.

It appears also that the irritation produced by the gas causes a contraction of the bronchial muscles. This tends to aggravate the effects of the desquamation of the terminal bronchi. If by the use of an anodyne the spasm could be reduced, the number of bronchioles remaining patent would be increased, and the administration of oxygen would become more effective. The inspiratory efforts would become less violent, and the tendency to emphysema would be reduced. Anything reducing the tendency to exudation such as, for instance, the injection of suitable quantities of sugar solution, might also be beneficial.

## Summary

1. Exposure to phosgene, like exposure to nitrous fumes, does not give immediate warning of the grave consequences which may supervene within twenty-four hours.

2. Phosgene does not act as a direct lethal agent, but as a powerful irritant to the air passages, setting up profuse

exudation and cellular desquamation which obstruct the terminal bronchioles.

3. The irritation also causes contraction of the bronchial muscles, associated with asthmatic symptoms.

4. Finally, the bronchioles become so firmly plugged that the entry of air into the alveoli becomes impossible; death then results.

5. Treatment should be directed to the reduction of the exudation and muscular spasm, and to increasing the value of the inspired air by the administration of oxygen.

# OBSERVATIONS ON THE RELIABILITY OF THE COMF-THERMOMETER (FRESH-AIR GAUGE) AS AN INDICATOR FOR THE COOLING EFFECT OF AIR*

H. I. Eadie, D. Hargood Ash, and T. C. Angus

PREPARED UNDER THE DIRECTION OF

LEONARD HILL, J. J. R. MACLEOD, AND J. SATTERLY

THE fresh-air gauge, or "comf," consists of a cylindrical metal box 18 cm. high and 10 cm. in diameter, in which is inserted an 8 candle-power carbon filament lamp, of known wattage, the lower part of the box being removable for this purpose. On the top of the box is fixed a metal cone which, in its turn, forms a union with a chimney 25 cm. long and 2½ cm. in diameter. There are some holes in the lower and upper part of the box for purposes of ventilation. An ordinary dry bulb thermometer is introduced into the chimney so that the bulb hangs centrally within it at a depth of 9 cm. The thermometer is attached to the top of a chimney by means of a suitable grip. Given a main current of suitable voltage which remains uniform, or which varies only slightly, the 8 candle-power lamp acts as a constant source of heat, while the box and the chimney are cooled by radiation and convection. The instrument is shown in Figure 1.

Observations were taken in Toronto by Miss Eadie in order (1) to obtain, if possible, a relation between the comf and kata-thermometer readings; (2) to determine the agreement between comfs taking the same current; (3) to test the results of altering the number of ventilation holes; (4) to test the rate of adjustment to varying conditions; and (5) to obtain, if possible, a relation between comf and kata in an air current.

*Observations to Obtain Relation between Comf and Kata-Thermometer Readings.*—The comf was set up in a small room and allowed to heat up until the reading became fairly steady. Then readings were taken at intervals of about five minutes. Kata-thermometer readings were taken simultaneously with those of the comf. Readings of kata and comf were then plotted against time. Figures 2 and 3 are typical of the large number of curves which were obtained in this way. The parallelism of the curves shows that changes in the condition of the air produce similar changes in both the comf and the dry kata-thermometer.

It was found that any disturbance of the wire gauze, which kept the thermometer central, produced a change in the readings. This gauze was, therefore, discarded, and the thermometer was suspended from a hook on the end of a rod which was soldered to the chimney of the comf. The lower end of the thermometer was fixed by means of a small spring of brass wire. New sets of readings were obtained similar to those already described and, from these, pairs of comf and kata readings were selected at random. Figures 4a and 4b show the straight lines obtained by using these

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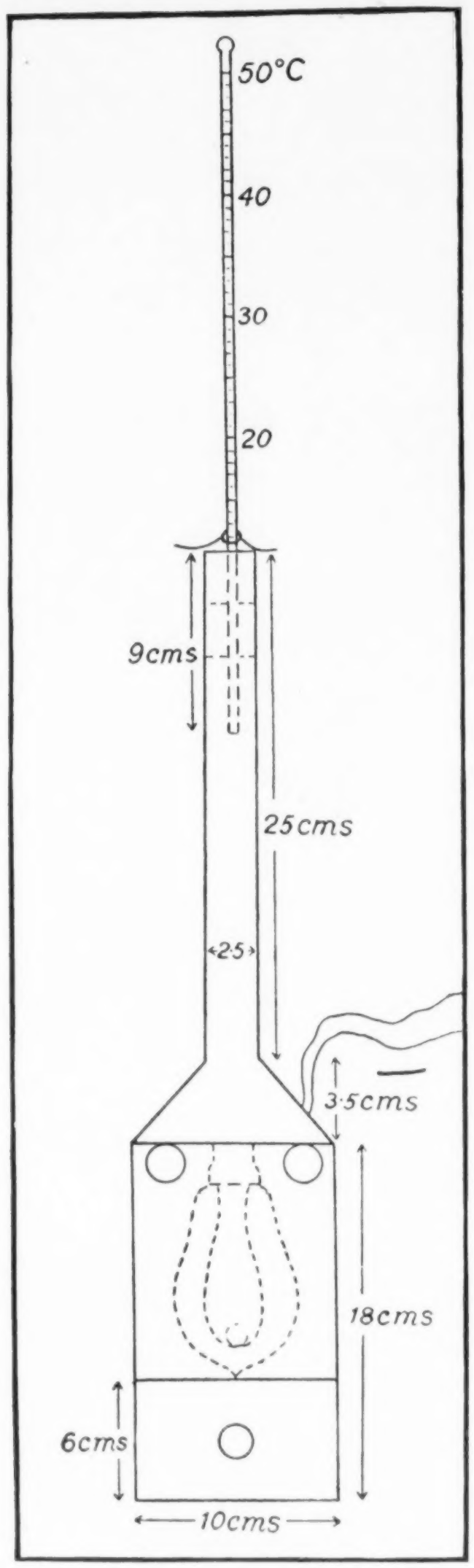



FIG. 1.—Fresh-air gauge or comf.

observations for currents of 0.195 amperes and 0.245 amperes, respectively, the two equations connecting the kata reading K and the comf reading C being $K = 18 - 0.29\ C$, and $K = 16.7 - 0.23\ C$.

Two comfs were set up in a lecture room, one at the back and the other at the front. During the classes readings were taken at the back at intervals of about five minutes, and at the front whenever possible. Readings of the kata-thermometer were taken simultaneously with those of the comf at the back. The current used was practically constant and the comf readings were expressed in millicalories per square centimeter per second by means of the equation obtained. These readings and the kata readings were plotted against time, and the results shown in Figure 5 were obtained. The unbroken line gives comfimeter readings; broken line, kata readings. It will be seen that in all but one case the two curves are almost exactly coincident. The comf at the front of the room always gave a reading about 10°C. lower than the one at the back.

*Agreement between Comfs Taking Same Current.*—Figure 6 shows the curves of three comfs all taking the same current, 0.280 amperes in the lamp. A and b are for comfs which were similarly made. C is for a comf, the chimney of which was painted black.

*Results of Altering Number of Ventilation Holes.*—The number of perforations in the conical part of a comf was increased and its curve again found. Figure 7 illustrates the results obtained. Points marked X were obtained from a comf with a single row of holes. Points marked (X) were obtained from a comf with a double row of holes. It is obvious that increasing the number of holes does not affect the ultimate height of the curve of the comf.

*Rate of Adjustment to Varying Conditions.*—The rate of adjustment to changing conditions was tested (1) with a single row of holes, and (2) with a double row of holes. Readings were

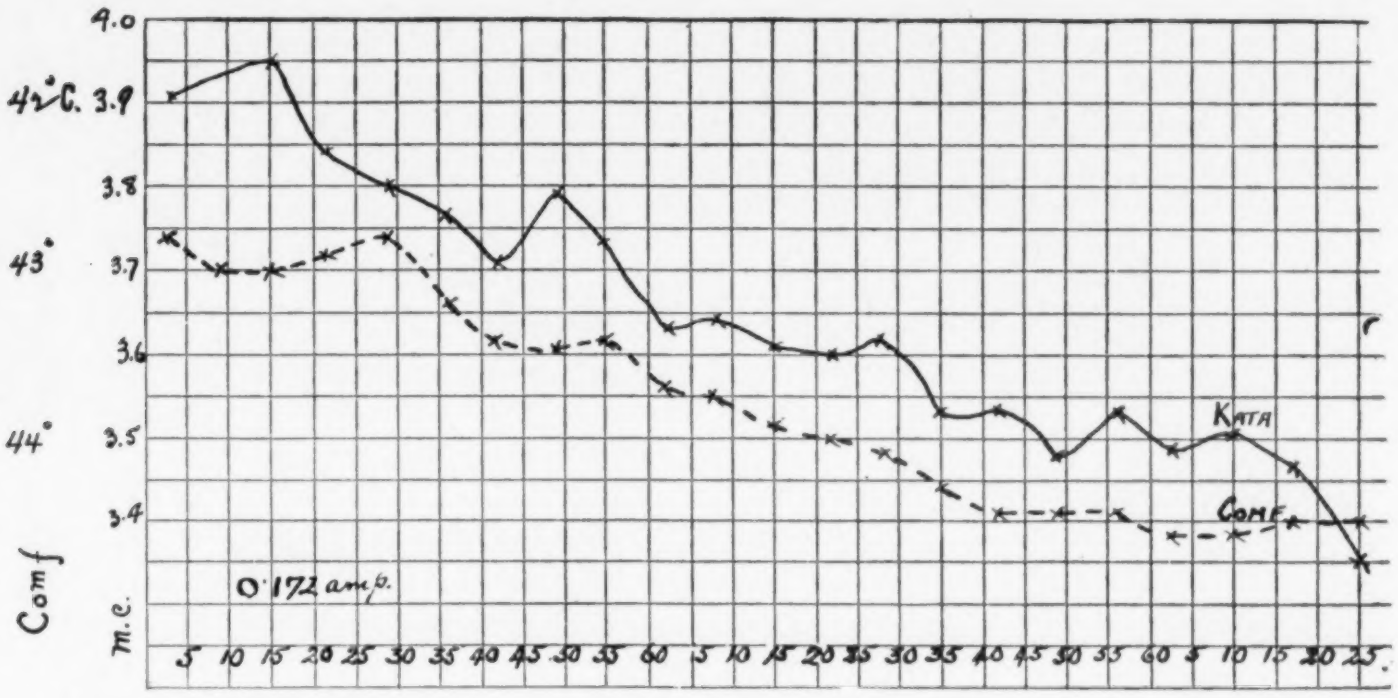



FIG. 2.—Variation with time of heat loss from kata and temperature of comf. Abscissas=time in minutes. Ordinates for kata readings=millicalories emitted per square centimeter per second; ordinates for comf readings=degrees centigrade.

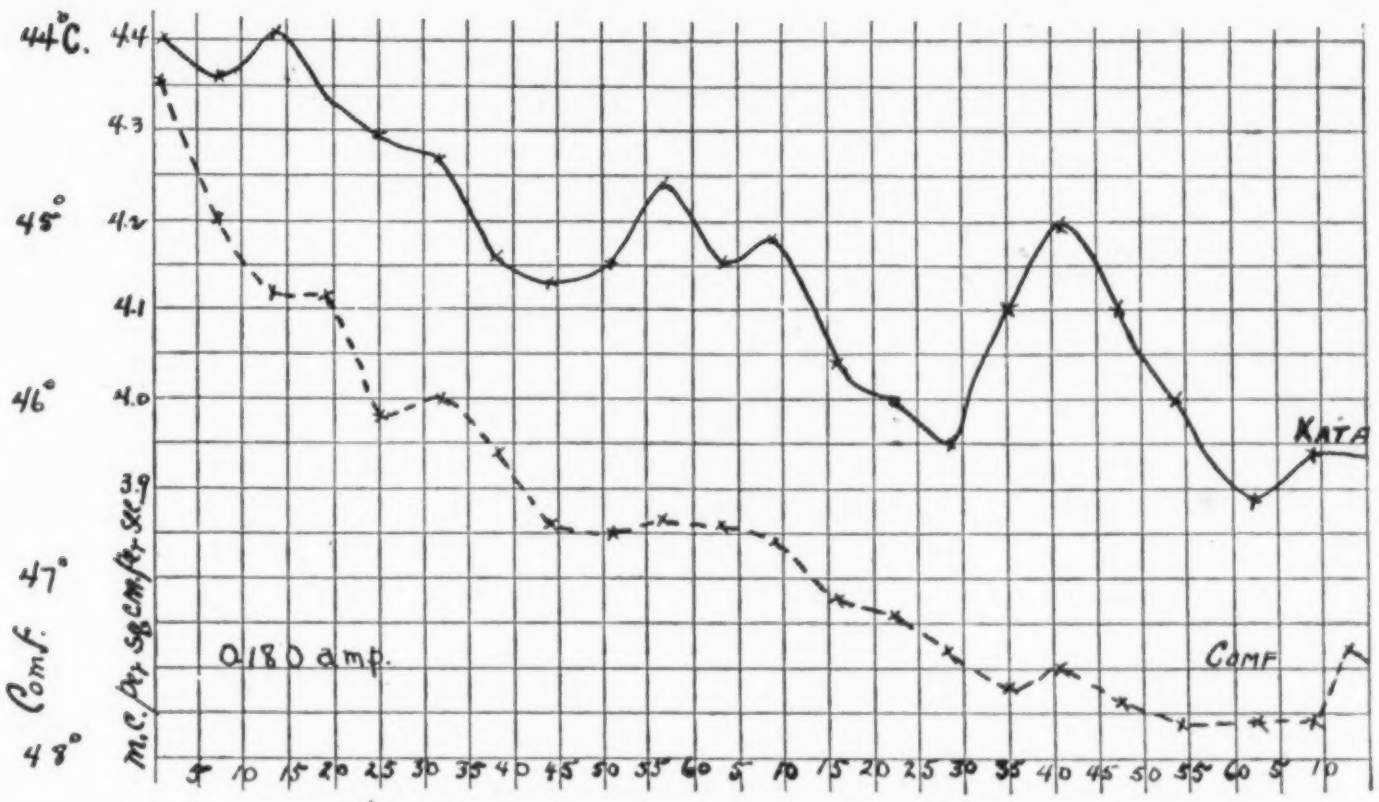


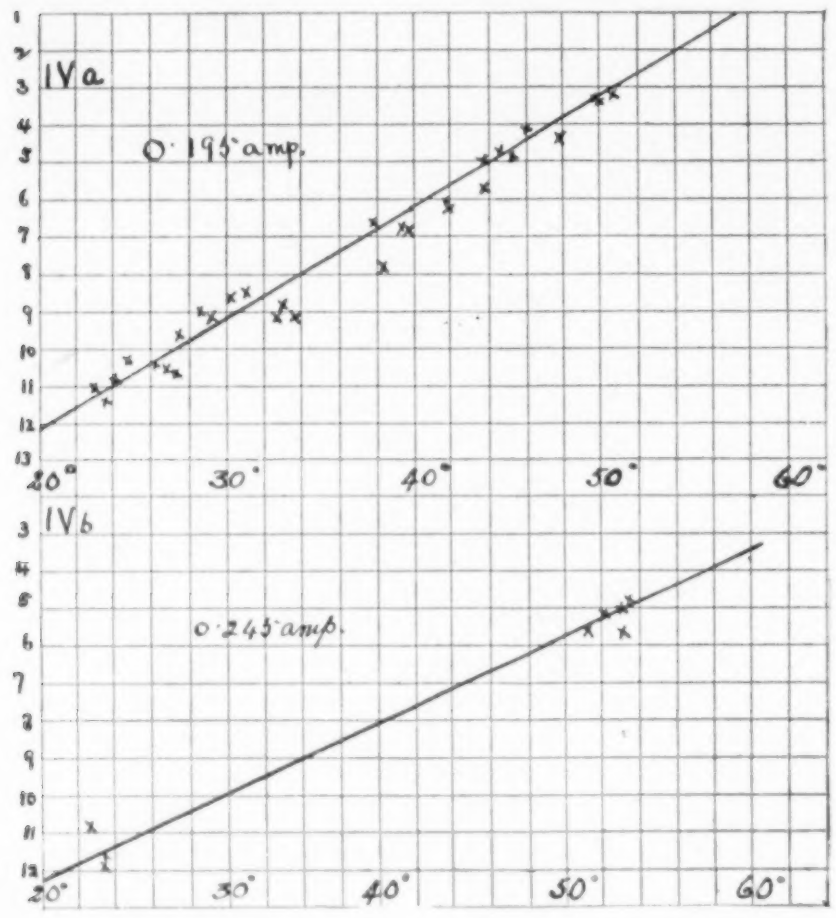

FIG. 3.—Variation with time of heat loss from kata and temperature of comf. Abscissas and ordinates the same as in Figure 2.

taken of the rate of fall of temperature of the comf thermometer in a draft *produced by a fan*. The results obtained are shown in Figure 8. In this chart, comf readings are plotted against time, so that the slope of the curve gives the rate of adjustment. The fact that the two curves are practically parallel shows that increasing the number of holes does not affect the rate of adjustment to changing conditions.

*Relation between Comf and Kata in Air Current.*—Figure 9 shows the results obtained by taking readings in different degrees of draft. The points marked F were taken in the draft (a large fan was used to produce the draft and conditions were such that both instruments were in the same current of air). The points marked S were taken in still air. This seems to indicate that a straight line is obtained between kata and comf readings in different degrees of draft *down to a certain limiting value* which would not be approached under ordinary conditions; and that this curve agrees very well with that obtained in still air (the dotted line in the chart).

The curve, of course, breaks down when a great degree of draft is reached, for at this point, if the line were continued, the kata reading would correspond with a comf thermometer reading lower than the temperature of the room, which is, of course, impossible.

The instruments used at Toronto were of unpainted tin; those used in later experiments were covered with black enamel. The wire gauze referred to in the observations to obtain the relation between comf and kata-thermometer was used in the early form of the instrument in order to keep the thermometer central in the chimney. As a result of these and similar experiments it was afterwards done away with and the thermometer was fixed rigidly at the top of the chimney.




FIGS. 4a and 4b.—Calibration curves of a comfimeter with different currents through the lamp. Abscissas=comf temperature in degrees centigrade; ordinates=millicalories emitted per square centimeter per second.

Observations were taken at Hampstead, London, by Mr. T. C. Angus in order to confirm and continue the results of Miss Eadie. A near approximation to a still air chamber was made by using a screen of American cloth

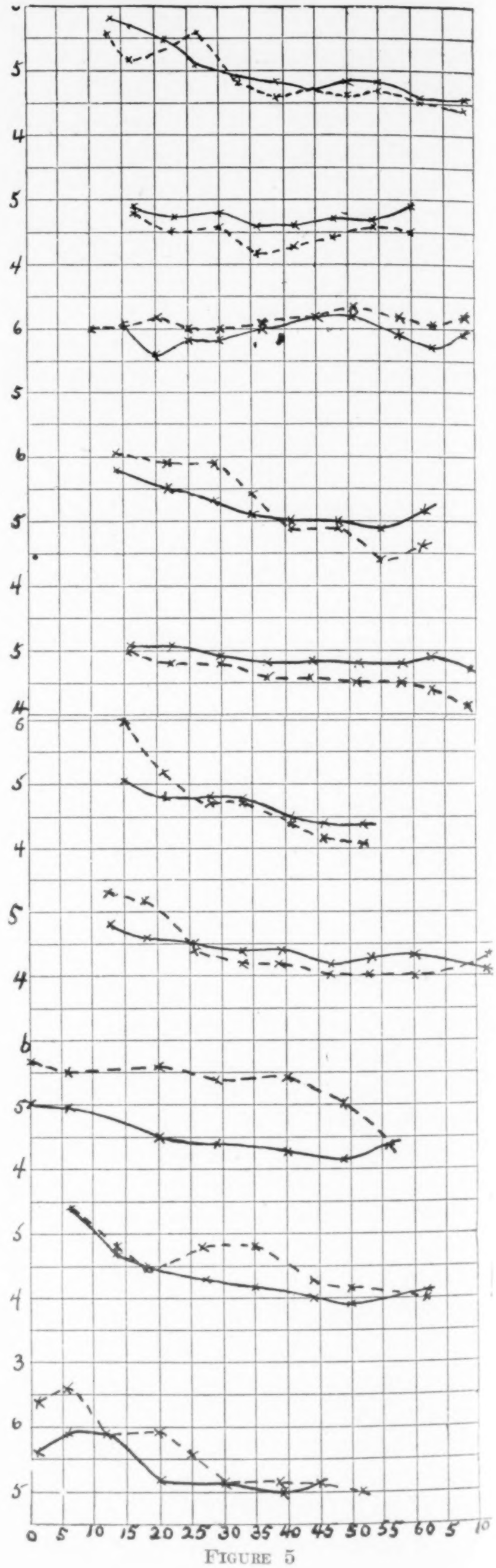



FIGURE 5

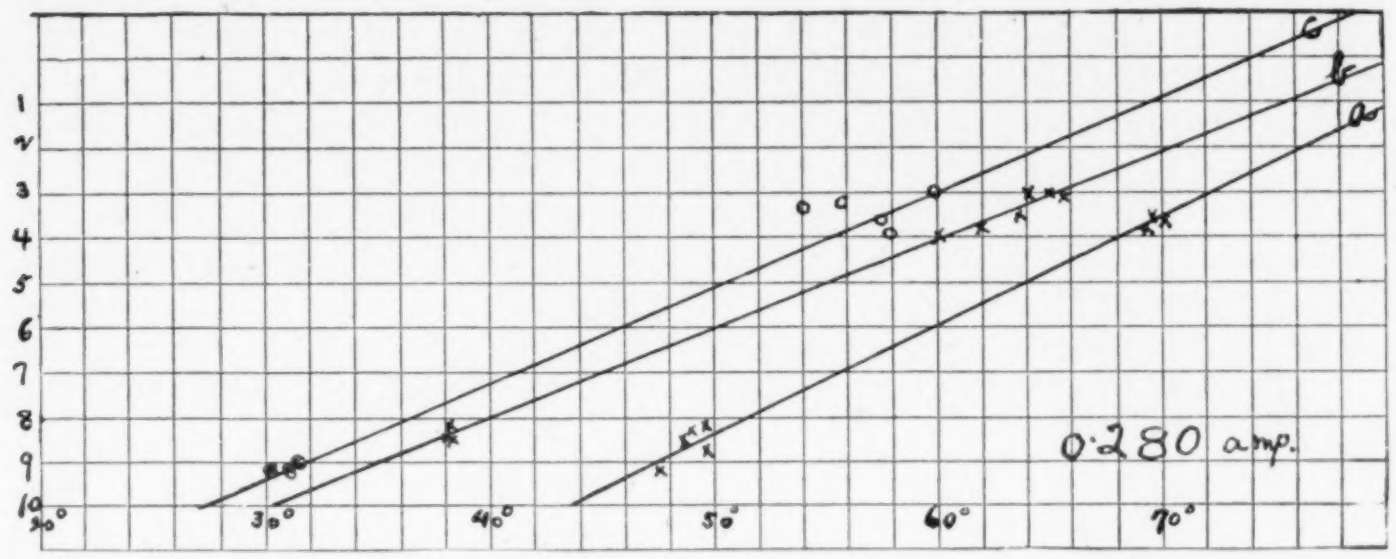



FIG. 6.—Determination of constant of comfimeter. Comparison of three comfimeters with a kata-thermometer under varying conditions. Abscissas= comf temperature in degrees centigrade; ordinates=kata reading in millicalories per square centimeter per second.

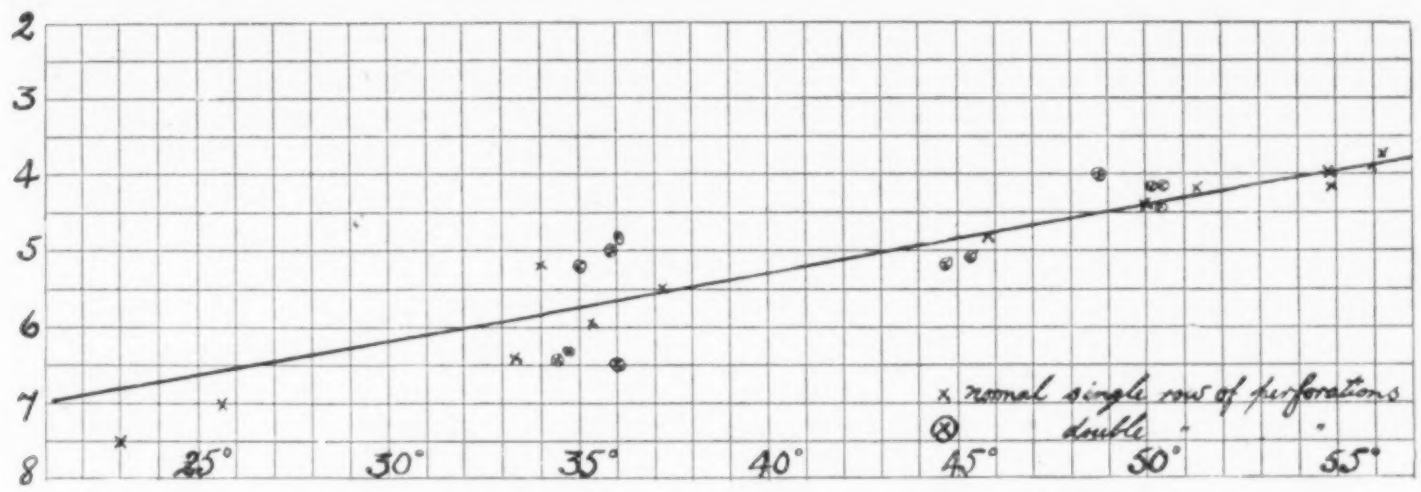



FIG. 7.—Comparison of kata readings with readings of comfimeter (1) having normal row of perforations (marked x); and (2) having double row of perforations (marked (x) ). Abscissas=comf. temperature in degrees centigrade; ordinates=heat loss.

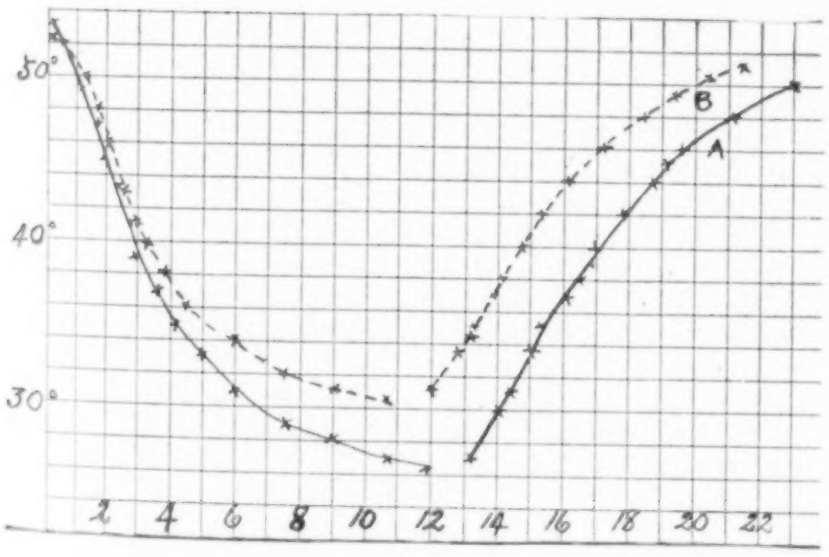



FIG. 8.—Behavior of two comfimeters, A and B. Fan turned on at beginning but stopped after twelve minutes. Abscissas=time in minutes; ordinates=comf temperature in degrees centigrade.

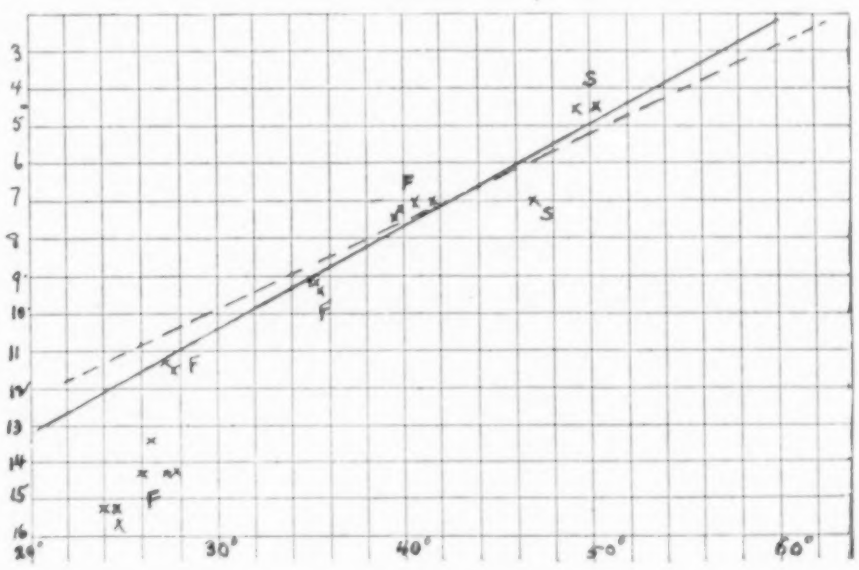



FIG. 9.—Determination of comfimeter constant by comparison with kata. Points xF indicate fan on; points xS indicate still air. Broken line shows a curve previously obtained. Abscissas=comf temperature in degrees centigrade; ordinates= millicalories per square centimeter per second.

enclosing a 4-foot square. This was open at the top and had a celluloid window let in all round about 1 foot from the top, for reading the instruments. Specially selected lamps of 33 to 35 watts were supplied by the Edison-Swan Electric Company both for 200 and 100 volt circuits.

Five comfs were fitted with thermometers which had been tested and were found to read together, and these were placed on a wooden support inside the screen. The connections were taken off in parallel from one lead. Table 1 gives the time, the temperature inside

and outside the enclosure, and the readings of the five comfs. It will be seen from the observations when A and B were interchanged that the slight variations were due to position. Figure 10

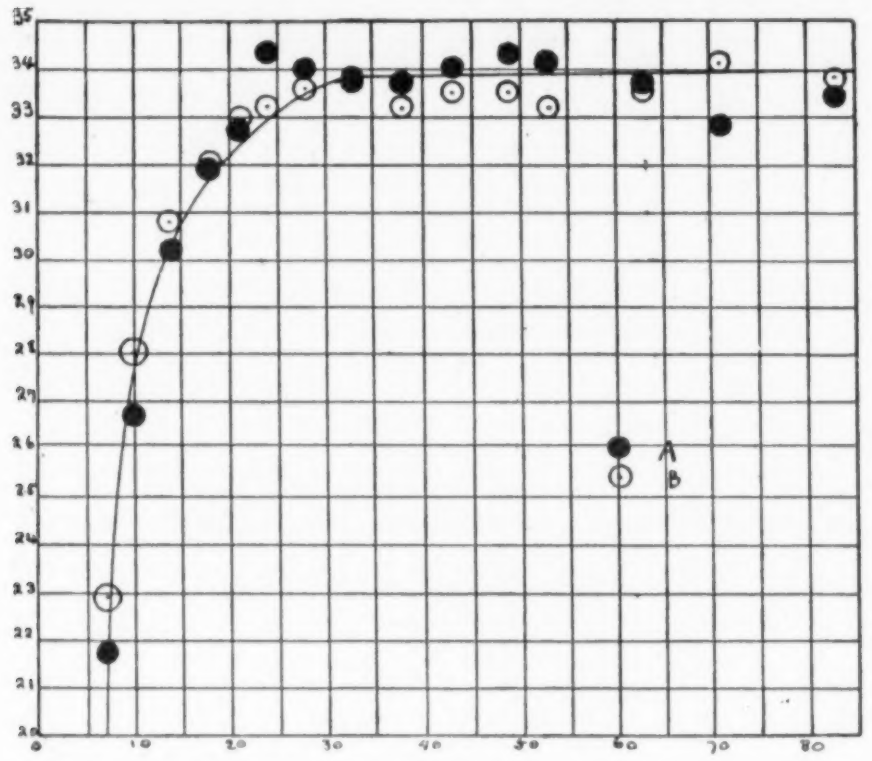



FIG. 10.—Comparative readings of two comfimeters, A and B, inside the same enclosure. Abscissas=time in minutes; ordinates=comf temperature in degrees centigrade.

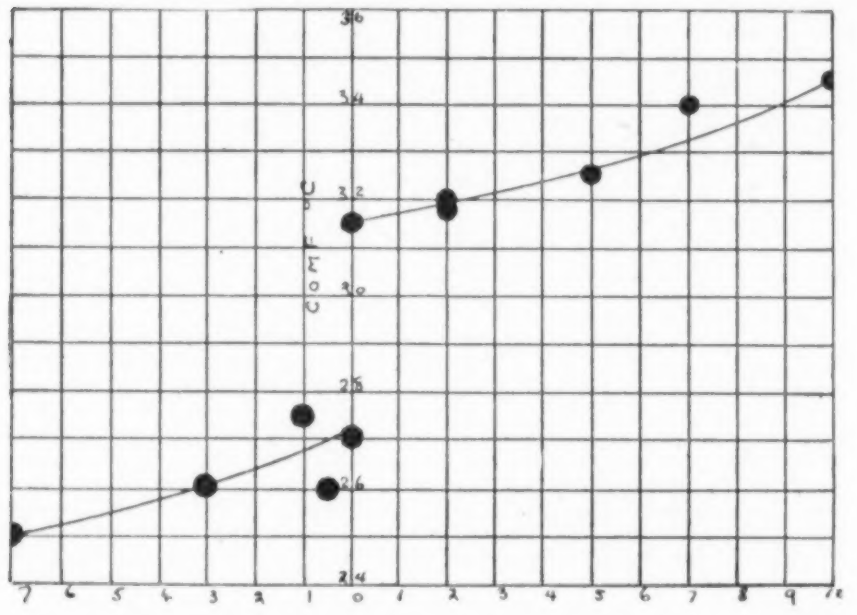



FIG. 11.—Showing rise of comfimeter reading with increase of voltage on lamp, and on a different day, fall of comf reading with decrease of voltage on lamp. Abscissas=percentage voltage variation; ordinates=comf temperature in degrees centigrade.

shows these observations plotted for A and B. The time during which they were taken was eighty minutes.

Observations were also taken within the screen in order to determine the effect of the variation of voltage, the temperature being approximately constant. From the results shown in Figure 11 it will be seen that a ± 6 per cent. voltage variation causes a difference of about 1.5° C. in comf reading.

Figure 10 also shows that about thirty minutes must be allowed for the comf to get in a steady state before the readings are taken.

Many observations taken at Hampstead confirm the conclusion drawn from the observations made at Toronto —namely, that in *still air* a linear relation exists between the kata and comf readings. Table 2 shows readings of both instruments taken at Hampstead, the comf being run off the ordinary lighting mains of the building. These mains are used for "lifts" and at times considerable variation in the voltage is experienced. As will be seen from Table 2, the observations were taken in various parts of different rooms. The equation obtained with these observations gives a relation between the cooling power H and the comf reading C, namely, $H = 16.8 - 0.35\ C$. The column H calculated gives the values obtained by using this equation to find H from the column C. These values give some idea of the variation that occurred.

It was found that no simple relation existed between the two instruments in a fast air current.

## CONCLUSIONS

From the foregoing observations we may conclude that the comf is a reliable instrument for indicating whether the air conditions are satisfactory, provided the following precautions are taken:

1. That specially selected electric light bulbs (33-35 watts) are used.
2. That a practically steady main line voltage is used.
3. That each instrument is calibrated before use against a kata-thermometer.

TABLE 1.—COMPARISON OF READINGS OF FIVE COMFIMETERS INSIDE THE SAME ENCLOSURE

| Time | Temperature | | Comfimeter | | | | |
|---|---|---|---|---|---|---|---|
| | Inside Enclosure | Outside Enclosure | A | B | C | D | E |
| *min.* | ° *C.* | ° *C.* | | | | | |
| 6 | 16.2 | – – | 21.7 | 22.9 | 21.7 | 22.0 | 21.8 |
| 10 | 16.7 | – – | 26.7 | 28.0 | 28.0 | 27.1 | 27.6 |
| 14 | 17.0 | 14.8 | 30.2 | 30.8 | 31.0 | 30.3 | 30.2 |
| 18 | 17.0 | 14.8 | 31.9 | 32.1 | 32.5 | 31.7 | 31.8 |
| 21 | 17.0 | 14.7 | 32.7 | 33.0 | 32.8 | 32.6 | 32.3 |
| 24 | 17.2 | 15.0 | 34.3 | 33.2 | 33.1 | 33.2 | 32.8 |
| 28 | 17.3 | 15.0 | 34.0 | 33.6 | 33.5 | 33.8 | 33.4 |
| 33 | 17.4 | 15.0 | 33.7 | 33.8 | 33.8 | 33.8 | 33.7 |
| 38 | 17.6 | 15.3 | 33.7 | 33.2 | 33.9 | 33.6 | 33.5 |
| 43 | 17.8 | 15.3 | 34.0 | 33.5 | 34.2 | 34.0 | 33.7 |
| 49 | 17.8 | 15.3 | 34.3 | 33.5 | 34.3 | 34.2 | 33.9 |
| 53 | 17.8 | 15.5 | 34.1 | 33.2 | 32.3 | 33.8 | 33.9 |
| 63[1] | – – | – – | 32.6 | 33.5 | 33.9 | 33.4 | 34.0 |
| 71 | – – | – – | 32.8 | 34.1 | 34.1 | 33.4 | 33.2 |
| 83 | – – | – – | 33.4 | 33.8 | 34.4 | 33.9 | 33.2 |

[1] The positions of A and B were interchanged here.

TABLE 2.—COMPARATIVE READINGS OF COMFIMETER AND KATA-THERMOMETER TAKEN IN VARIOUS PARTS OF DIFFERENT ROOMS

| H Calculated | Comfimeter C | Kata H | Location of Instrument during Observations |
|---|---|---|---|
| 6.5 | 29.56 | 6.81 | 2 feet from floor; no direct air current on instrument. |
| 5.0 | 33.90 | 4.67 | Instrument screened from direct draft; at waist level. |
| 6.2 | 30.48 | 6.43 | At side of room remote from open windows; at waist level. |
| 6.1 | 30.70 | 6.20 | At side of room remote from open door; on floor. |
| 6.7 | 28.56 | 6.00 | In middle of floor; window open 3 inches. |
| 6.3 | 30.23 | 6.00 | In middle of floor; window wide open. |
| 5.4 | 32.70 | 5.40 | Between two open doors, on bench 3 feet from floor. |
| 6.0 | 30.96 | 6.00 | Window and two doors open; on table 3 feet from floor. |
| 6.1 | 30.70 | 5.70 | On floor. |
| 5.1 | 33.60 | 4.98 | 3 feet from floor. |
| 4.6 | 34.90 | 4.70 | " " " " |
| 5.3 | 32.90 | 6.60 | On floor. |
| 5.0 | 33.90 | 6.80 | " " |
| 5.7 | 31.90 | 5.60 | 4 feet from floor. |
| 3.9 | 36.90 | 4.70 | " " " " |
| 5.1 | 33.50 | 5.20 | On floor. |

Since the relation between the instruments is linear, observations should be taken at three different still air temperatures, the results should then be plotted and a straight line drawn through them; the equation of this line will then be the equation connecting the readings.

4. That the instrument is not used in a fast air current.

# THE PHARMACOLOGY OF SOME PHENYLENEDIAMINES
(*Continued*)

PAUL J. HANZLIK, M.D.

*Professor of Pharmacology, School of Medicine, Stanford University*

*(From the Departments of Pharmacology, Stanford University, San Francisco, and Western Reserve University, Cleveland)*

### 6. *Circulation*

The effects of the phenylenediamines on the circulation have not been previously studied. The results of this study indicate that they possess definite and marked actions on the circulation. A knowledge of these actions is essential in cases of acute and chronic poisoning and in cases of death from these compounds. The experiments consisted of intravenous injections in mammals; perfusion of turtles' hearts, perfusion of frogs' vessels, and treatment of strips of dog's ventricle and excised vessels with the compounds.

*Injection Experiments.*—Observations were made on sixteen dogs, two rabbits, and one cat. All injections were made intravenously. The compounds were used in their basic form and in the form of hydrochlorides, dissolved or suspended in 0.9 per cent. sodium chloride solution. The effects of the hydrochlorides were the same as those of the bases. The following functions were observed: pulse rate; mean blood pressure from the carotid artery recorded by a mercury manometer in the usual way; cardiac (ventricular) volume by means of the ball plethysmograph of Y. Henderson; and kidney volume from an oncometer. All records were made simultaneously on a slowly moving kymograph. At the same time the majority of animals were curarized and artificial respiration was maintained. This was necessary because of disturbances from convulsions which ensued promptly unless curare was injected. Small and large doses of the compounds were used, usually repeatedly in the same animal, and the analysis was carried as far as possible in order to ascertain the mechanism of action on the circulation, exclusive of the convulsant and other actions.

It may be stated at once that the results with the different phenylenediamines studied were qualitatively the same; they differed only quantitatively —that is, the meta and para compounds were weaker than the dimethyl and diethyl derivatives of para-phenylenediamine, while dimethyl-para-phenylenediamine was the strongest of all. Detailed descriptions are, therefore, omitted. Figure 2 illustrates the effects of meta-phenylenediamine (the weakest compound), and Figure 3 the effects of dimethyl - para - phenylenediamine (the strongest compound) upon the circulation of dogs.

Immediately after the intravenous injection of moderate doses of 0.5 c.c. to 1 c.c. of 1 per cent. per kilo of the phenylenediamines there was a temporary fall of blood pressure, a decrease in the pulse rate, an increase in cardiac volume (diastolic tendency), and diminution in kidney volume. These effects lasted from one-half to one minute, and were followed by a complete recovery of all functions. One to two minutes later

there was a marked increase in pulse rate, with diminution in cardiac volume (systolic tendency), a rather marked and sustained rise of blood pressure lasting from ten to fifteen minutes, and an increase in kidney volume as long as the pulse rate and blood pressure remained increased. After fifteen to twenty minutes, all functions returned to their original conditions. These changes occurred with blood pressures below and above the shock level. With repeated small doses, and with very large single doses the depressor action predominated; the heart stopped in diastole and could not be revived by the usual resuscitative measures—direct electrical stimulation, increase in coronary pressure, cardiac massage, injections of epinephrine, digitalis, caffein, 6 per cent. acacia, and 0.9 per cent. sodium chloride. As a rule the heart appeared very dark. The auricles continued to beat, while the ventricles remained permanently inhibited. Occasionally ventricular fibrillation was observed at the end of the experiment. The effects were uninfluenced by previous section and atropinization of the vagi, and therefore were not due to depression of vagus function. The lowest effective intravenous dose of meta-phenylenediamine was about 0.006 gm. per kilo; of the meta and para compounds about 0.017 gm. per kilo were required for definite and sustained action. The just effective dose of dimethyl-para-phenylenediamine was about 0.003 c.c. per kilo, of diethyl-para-phenylenediamine, 0.005 c.c. per kilo.

The effects of the phenylenediamines on the circulation resemble those of caffein and pituitary extract injected intravenously, and are mainly cardiac. The initial or immediate effects are due to direct cardiac depression, since all the changes are in the same direction—slowing of the pulse, cardiac dilatation, fall of blood pressure, and diminution in kidney volume. The depression from small doses is fleeting and is presumably due to reflex stimulation of the depressor nerve from local irritation of the endocardium by these compounds, which are powerful irritants for all tis-

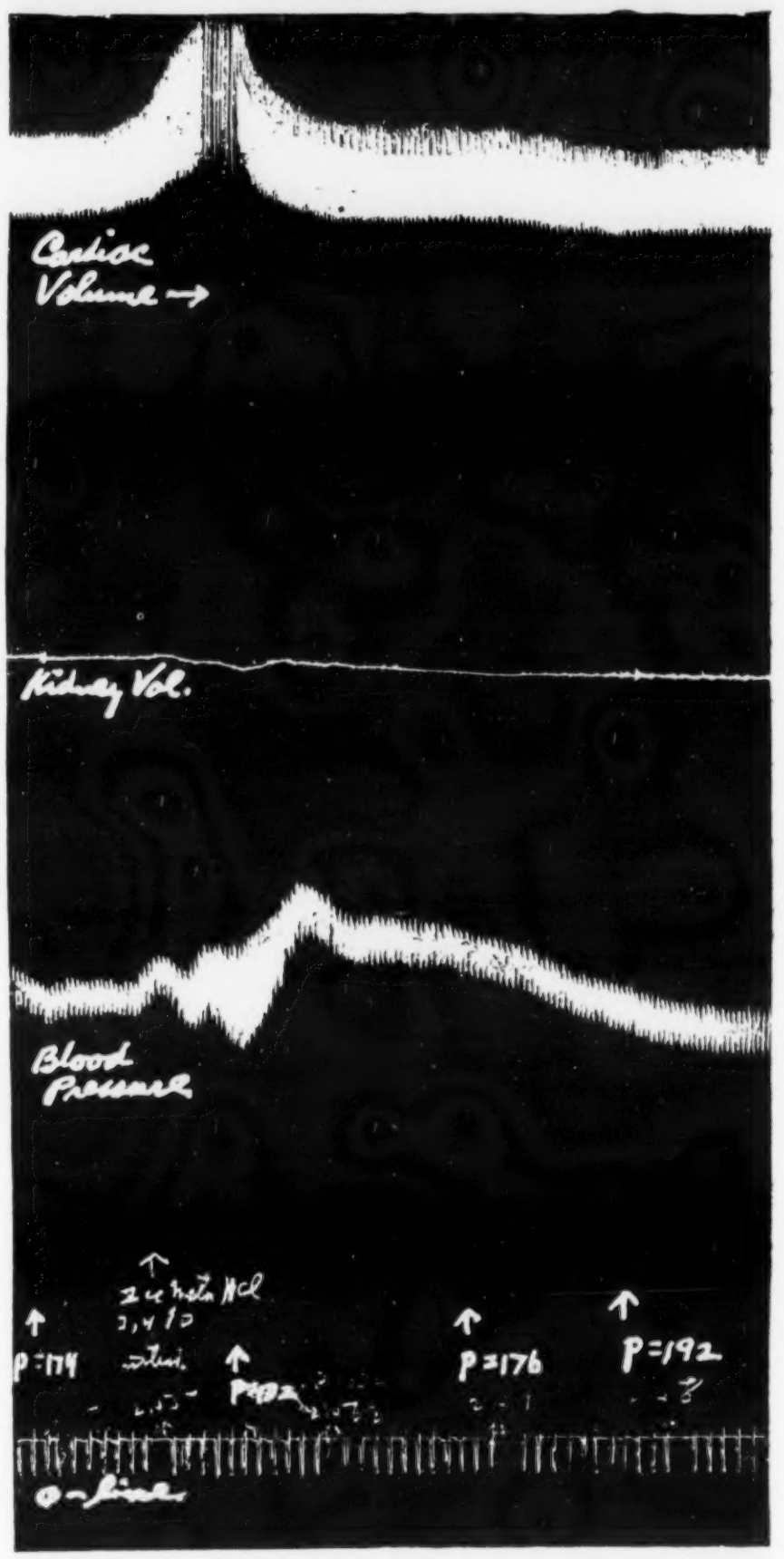



FIG. 2.—Effect of meta-phenylenediamine hydrochloride (0.0062 gm. per kilo injected intravenously) on the circulation of a curarized dog (11 kg.). Shows the moderate rise of blood pressure; initial slowing of pulse, and cardiac dilatation followed by increase in pulse rate and systolic tendency of the heart. Very little change in kidney volume. P=pulse rate. Time required for each stroke= five seconds.

sues. The depression cannot involve the vagus mechanism since it occurs after section and atropinization of the vagi. The later action is due to direct cardiac stimulation, since the changes are again in the same direction—increase in pulse rate, systolic tendency of the heart, sustained rise in blood pressure, and increase in kidney volume. Since there is an increase in kidney volume, the effects cannot be due to sympathetic stimulation unless the phenylenediamines possess specific renal vascular dilator effects. This does not seem to be the case, however, since all excised vessels, including the renal artery, are constricted. The pressor effects appear, therefore, to be due to direct cardiac stimulation. This supposition is further sustained by the augmentor effects observed on perfused turtles' hearts and strips of dog's ventricle. The toxic or final action con-

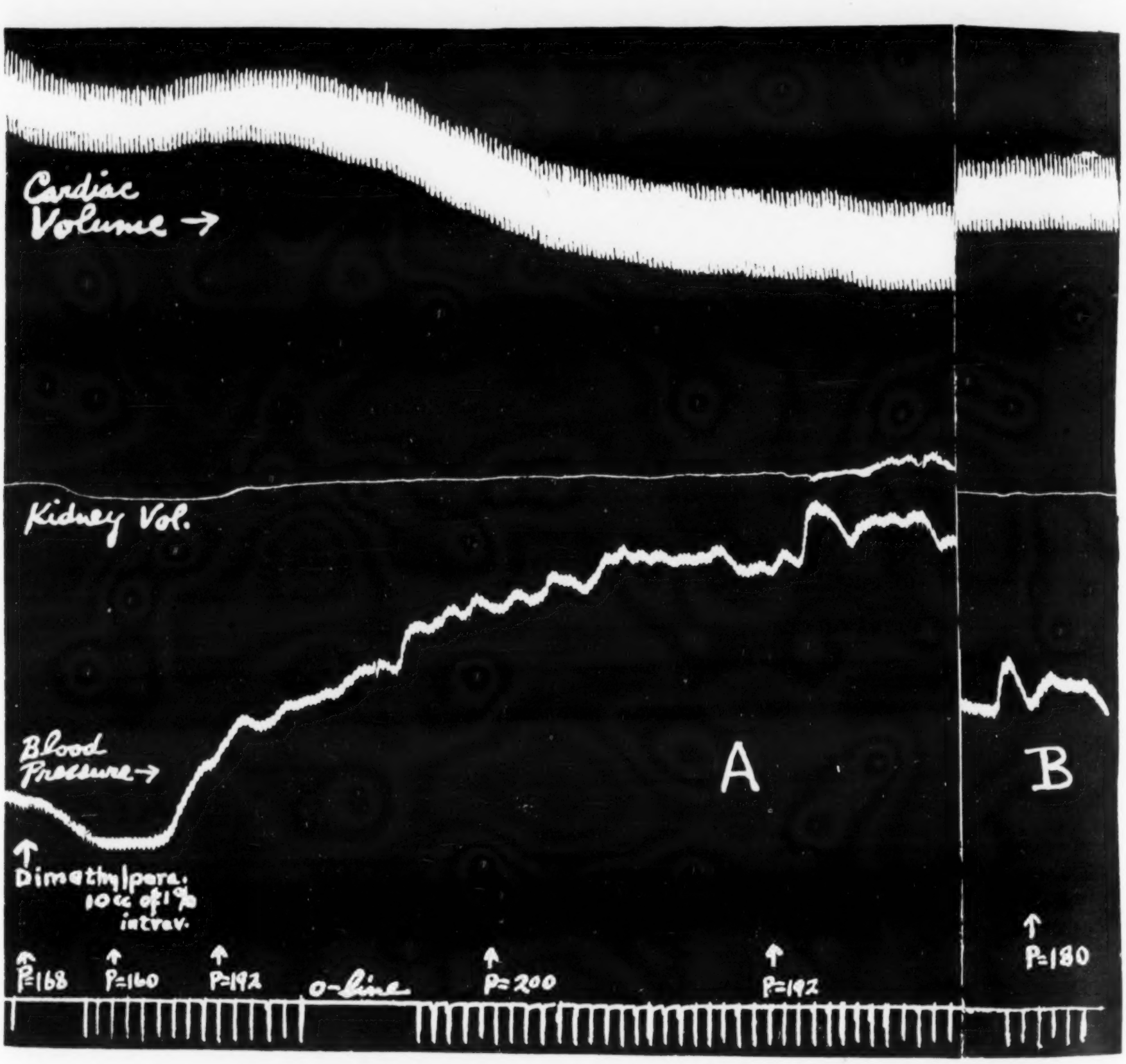



FIG. 3.—Effect of dimethyl-para-phenylenediamine (0.008 gm. per kg. injected intravenously) on the circulation of a curarized dog (12.5 kg.). (A) shows the initial fall of blood pressure with diastolic tendency of the heart, and diminution in kidney volume, followed by marked and sustained rise in blood pressure, systolic tendency of the heart, and increase in kidney volume. (B) Recovery was not quite complete at the end of fifteen minutes after injection; remained the same at the end of thirty minutes when other injections were made. P=pulse rate. Time required for each stroke=five seconds.

sists of direct cardiac depression and, finally, paralysis with death.

*Turtles' Hearts.*—The hearts of turtles were perfused *in situ* in the usual way, that is, an outflow cannula was placed in one of the aortas and an inflow cannula in a vena cava, and Ringer's solution to which the compounds were added in different concentrations was used. At the same time a record of the contractions was made on a slowly moving kymograph. The results on both untreated and atropinized hearts consisted of increase in tonus with some diminution in amplitude and acceleration of rate with concentrations of 1:20,000 to 1:10,000; and a fall of tonus, increase in amplitude, slowing of the pulse, and finally complete relaxation with standstill in the diastolic position with high concentrations (1:1,000). This is confirmative of the effects in mammals from the intravenous injection of small and large doses.

*Dog's Ventricle.*—Strips of ventricle from an atropinized dog's heart were immersed in warm, oxygenated Locke's solution, and contractions were recorded on a slowly moving kymograph; the ordinary arrangements for excised organs were used. The only effect observed was a gradual and sustained increase in tonus.

*Peripheral Vessels of Frogs.*—The vessels of frogs' extremities were perfused according to the Läwen-Trendelenburg technic. The effects of the dimethyl and diethyl derivatives of para-phenylenediamine were stronger, and are illustrated by Figure 4. The meta and para compounds were weaker, though qualitatively the effects were the same.

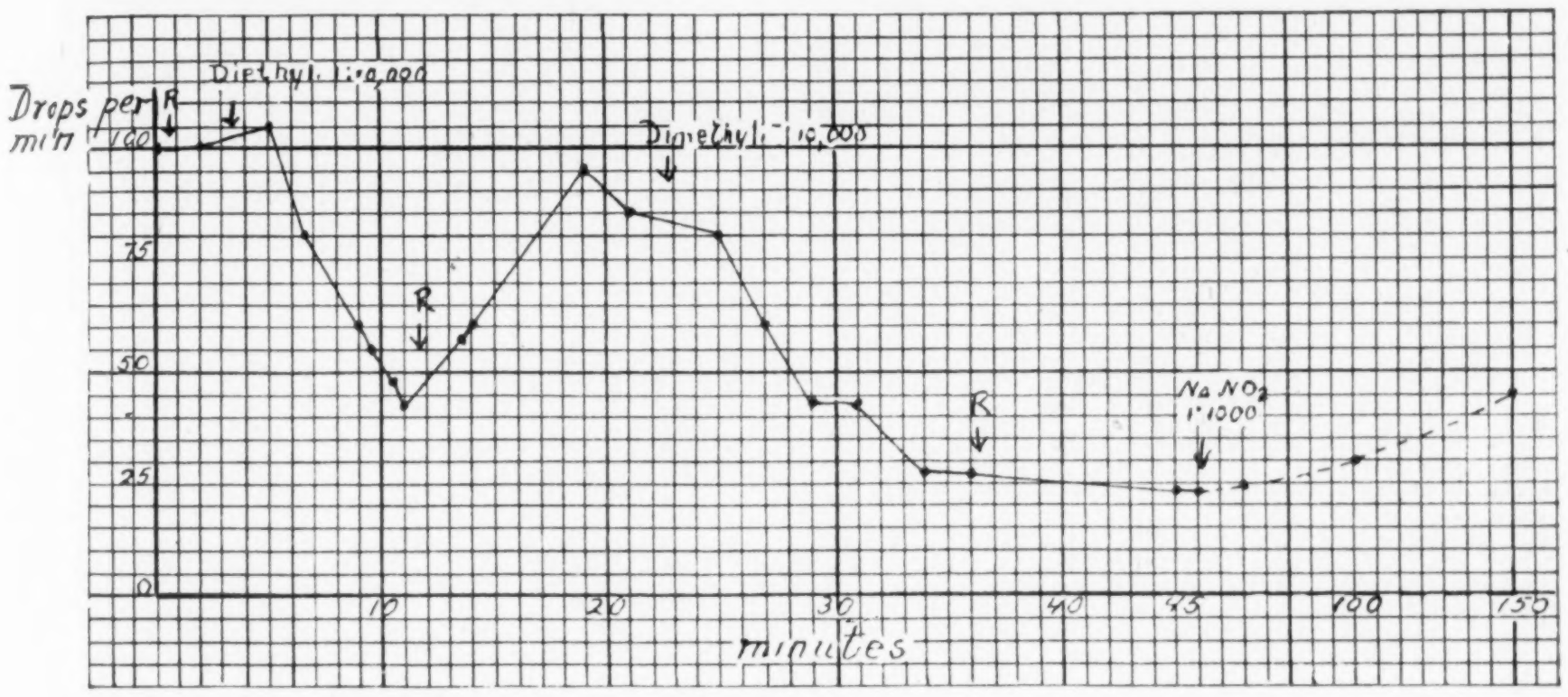



FIG. 4.—Constriction of blood vessels of frog's extremities by perfusion with diethyl-para-phenylenediamine (diethyl: base) and dimethyl-para-phenylenediamine (dimethyl: base). Constriction partly relieved by nitrite. R=frog's Ringer solution.

The effects consisted of constriction, and thus agreed with the effects on rings of excised arteries and aorta, which will be described later. The concentrations that were used ranged from 1:20,000 to 1:5,000, and the constrictions produced by these concentrations were removed by washing with plain Ringer's solution. As a rule the constrictions were antagonized by 0.1 per cent. nitrite. These results indicate that the rise of blood pressure observed after intravenous injection of small and moderate doses of

these compounds may be due at least in part, though not entirely, to a peripheral vasoconstriction. It will be recalled that the kidneys in injection experiments usually showed an increase in volume indicating a vascular relaxation, while excised renal artery was constricted. This simply means that the vessels in intact mammals play an uncertain, and presumably minor, rôle in the pressor action of the phenylenediamines, and that the main action depends upon the marked cardiac stimulation.

### 7. *Respiration*

The main effect of the phenylenediamines on respiration consisted of an increase in rate. This was observed after hypodermic and gastric administrations in intact dogs, cats, rabbits, white rats, and guinea-pigs. The wheezing, asthmatic respiration occurring in rabbits with edema of the tongue and neck from para-phenylenediamines was attributed by Erdmann and Vahlen, and Meissner to edema in the upper respiratory passages, including the glottis. The edema is undoubtedly a factor in this, since tracheotomy with the introduction of a cannula in the trachea gives marked relief. My experiments on bronchial tone indicate that there is also some bronchial constriction. This will be described in the next section.

Intravenous injection in dogs and cats, whose respiration was recorded by means of a tambour joined to a large T-tube in the trachea, showed that there was principally an increase in rate immediately after injection, followed by a slower respiration of greater depth. This occurred during the initial depressor action, and the respiratory change was the result of a brief period of anemia. When the blood pressure recovered and rose above the previous level, there was a recovery of the respiratory rate and volume to the previous condition. Further injections of the phenylenediamines usually resulted in tremors and convulsions with corresponding disturbances in respiration; as the convulsions subsided the respiration also recovered.

In rabbits, the respiratory rate and volume were reduced during the depressor action and increased when the blood pressure rose above the previous level. This augmentation in respiration continued until the level of blood pressure was again changed. With continued injections, convulsions supervened and markedly disturbed the respiration in the usual way. Fatal doses finally stopped the respiration altogether.

### 8. *Effects on Smooth Muscle*

The effects of phenylenediamines on smooth muscle are described for the first time in this paper. They were observed on excised and intact organs. The following organs were used: frog's stomach, esophagus, and bladder; intestine, uterus, and bladder of rabbits; pig's ureter; pupil of frog's excised eye, and intact eye of rabbit; intact bronchi of dog and guinea-pig; and excised aorta of rabbit and renal artery of dog. A great many experiments were made and the excised organs were treated in various ways for the purpose of analyzing the mechanism of the actions produced.

With excised intestine, uterus, bladder, ureter, and esophagus, longitudinal strips were made and suspended in warm, aerated Tyrode's solution, and records were made directly on a slowly moving kymograph. Frog's stomach was used in the form of ring preparations from the fundus. Aorta and renal

artery were also used in the form of rings. The enucleated frog's eyes were placed into little rings made from rubber tubing, and the solutions were applied directly. The experiments on bronchial tone will be described separately. It will be impossible to present records from all organs and under different conditions; instead, however, descriptive summaries with illustrative tracings of the actions on the uterus, bladder, and intestine will suffice. The differences in the various compounds will also be discussed briefly. Figures 5, 6, 7, 8, and 9 indicate typical effects with meta-phenylenediamine and para-phenylenediamine and the dimethyl and diethyl derivatives of para-phenylenediamine.

It was found that the phenylenediamines possessed definite and powerful actions on smooth muscle. Qualitatively, the responses with the different compounds studied were practically the same, except in the case of the pupil; they differed quantitatively, however. This difference will be discussed presently.

*Intestine, Uterus, Stomach, Ureter, Bladder, and Excised Artery.*—The action of the phenylenediamines on the excised stomach and intestine occurs in two stages. The first, or initial stage, occurs immediately after the application of the compounds. It is characterized by a fleeting depression of the tonus and amplitude of the contractions, and a slowing of the rate, contractions being barely perceptible with meta-phenylenediamine, definitely present with para-phenylenediamine and diethyl-para-phenylenediamine, and most pronounced with dimethyl-para-phenylenediamine. This depression usually lasts from one-half to one minute, but may last as long as five minutes if dimethyl-para-phenylenediamine is used. It was generally absent with strips of excised renal artery, aorta, uterus, ureter, and bladder. In other words, the temporary depres-

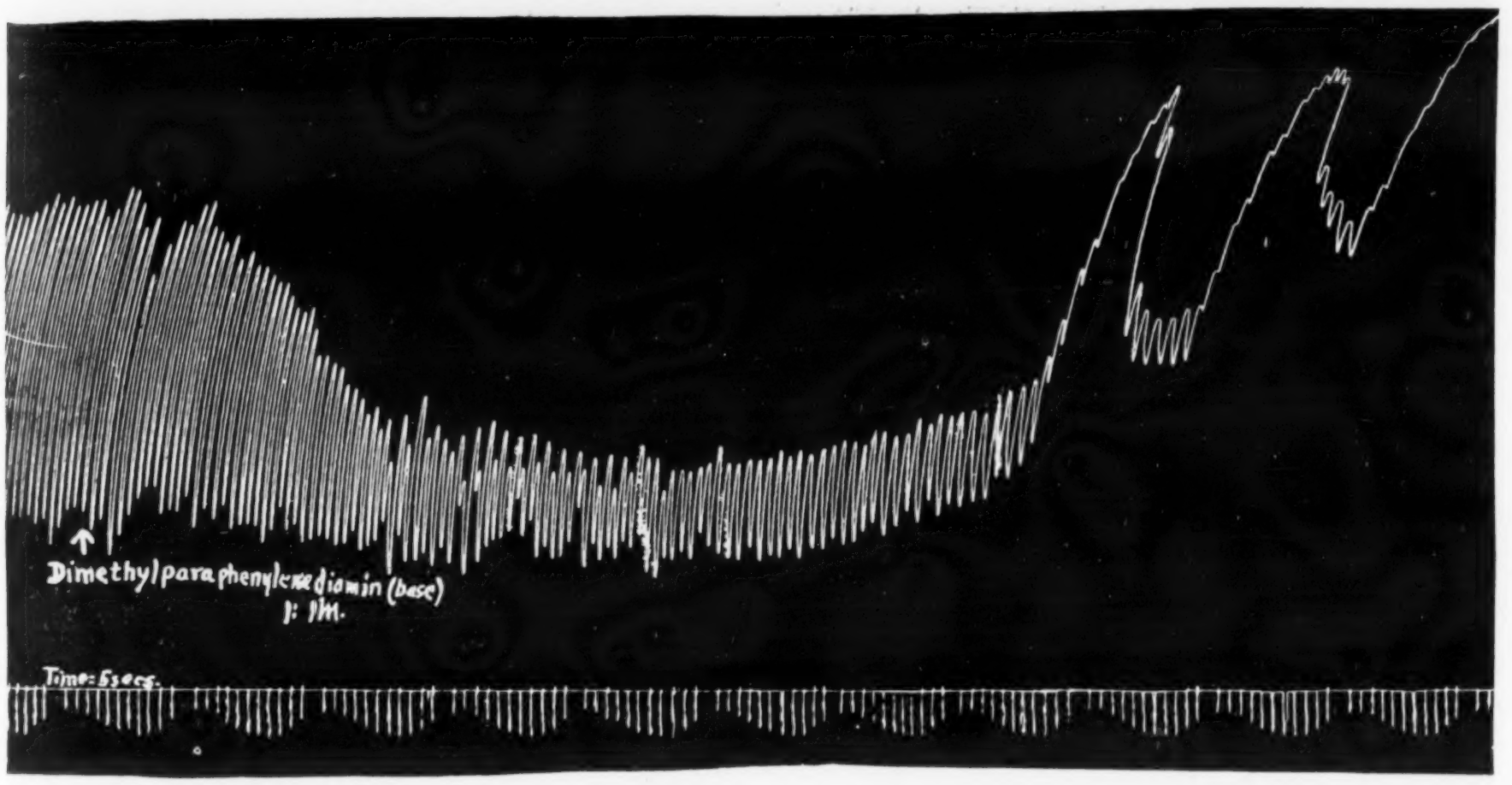



FIG. 5.—Effects of dimethyl-para-phenylenediamine (1:1,000 of base) on longitudinal strip of untreated rabbit's intestine in 50 c.c. of Tyrode's solution at 39° C. Time required for each stroke=five seconds. Shows depression for six minutes, followed by marked tonus augmentation which lasted for the next ten minutes, then gradually fell and was slightly lowered by atropine and epinephrine.

sion appeared to occur with those organs (intestine and stomach) which are innervated by inhibitory sympathetic fibers. The same occurred after preliminary treatment of these organs with apocodeine, which, according to some investigators, should exclude the sympathetic fibers from the site of action. The temporary, initial depression of the

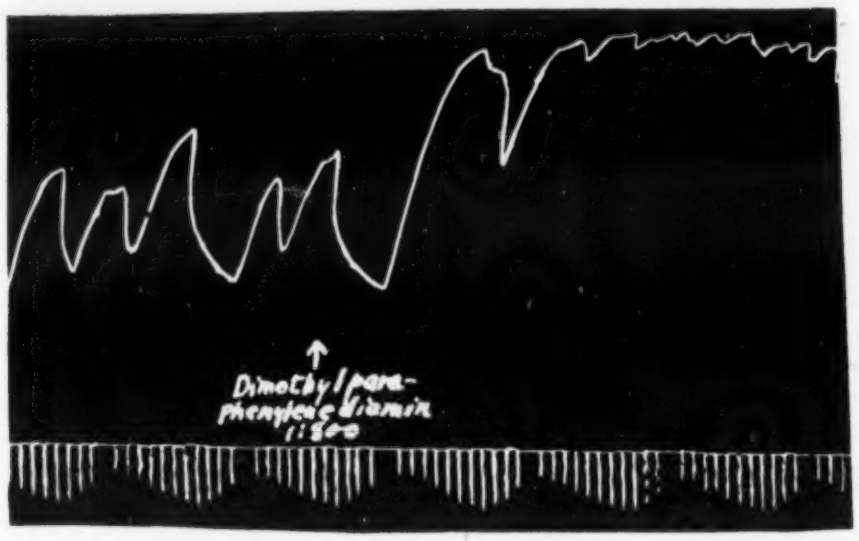



FIG. 6.—Effect of dimethyl-para-phenylenediamine (base, 1:800) on untreated pregnant uterus of cat in Tyrode's solution. Time required for each stroke=five seconds. Shows marked increase in tonus and rate of peristalsis which lasted for ten minutes.

intestine and stomach was followed by a much more pronounced and sustained augmentor action on all the organs studied. This constituted the second or principal stage of action on the intestine and stomach, and the only action on the uterus, artery, ureter, and bladder (also bronchi). The eventual effect of high concentrations was depression and paralysis of all organs.

The principal action of the phenylenediamines on organs containing smooth muscle consisted of a marked and lasting increase in tonus, with corresponding diminution in amplitude and a slight but variable increase in the rate of contractions. This action was most pronounced with dimethyl-para-phenylenediamine, and least (tonus augmentation) with meta-phenylenediamine. Meta-phenylenediamine caused principally an increase in amplitude of contractions of the intestine, uterus, stomach, and ureter, which lasted from five to ten minutes. There was no increase in tonus in any of the organs (except in the excised artery) and then it was barely detectable. Para-phenylenediamine produced a moderate increase in tonus of all organs, and diethyl-para-phenylenediamine caused a still further increase, while dimethyl-para-phenylenediamine was the most powerful of all. This gradation in tonus action of the phenylenediamines agrees in general with their toxicity and actions upon other functions—that is, meta-phenylenediamine is the least powerful, the para compound the next, then diethyl-para-phenylenediamine, and finally, dimethyl-para-phenylenediamine which is the most powerful. As would be expected, the diminution in amplitude and rate of contractions was proportional to the tonus increasing action of these compounds, and was least pronounced with meta-phenylenediamine and most pronounced with dimethyl-para-phenylenediamine.

The tonus augmentor action suggested that the mechanism of the action of para-phenylenediamine was on the muscle itself. This proved to be the case, since it occurred after exclusion of the ganglia and nerve endings by previous treatment of the organs with nicotine, atropine, and apocodeine, and also after inhibition of the intestine by epinephrine. Atropine and epinephrine only slightly depressed the marked increase in tonus of some preparations, and left others entirely unaffected. On the other hand, the increase in tonus was promptly abolished by chelidonine and papaverine, whose actions were on the muscle exclusive of nerve endings. It is concluded, therefore, that the mechanism of tonus augmentation in excised uterus, intestine, stomach, ureter, bladder, and

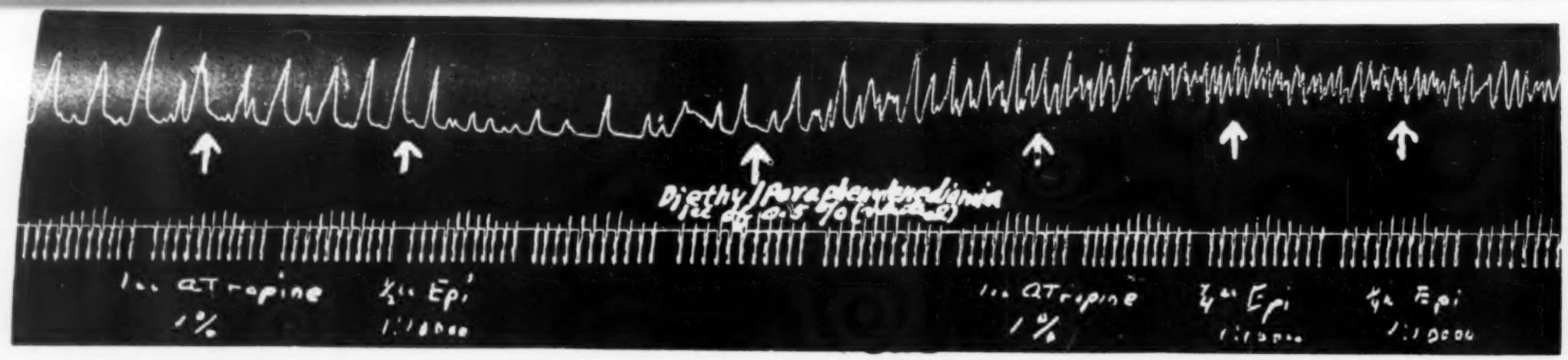



FIG. 7.—Effect of diethyl-para-phenylenediamine (neutral, 1:30,000) on strip of guinea-pig's bladder previously treated with atropine and epinephrine. Time required for each stroke = five seconds. Shows increase in rate and tonus and diminution in amplitude uninfluenced by later treatment with atropine and epinephrine. Epi = epinephrine.

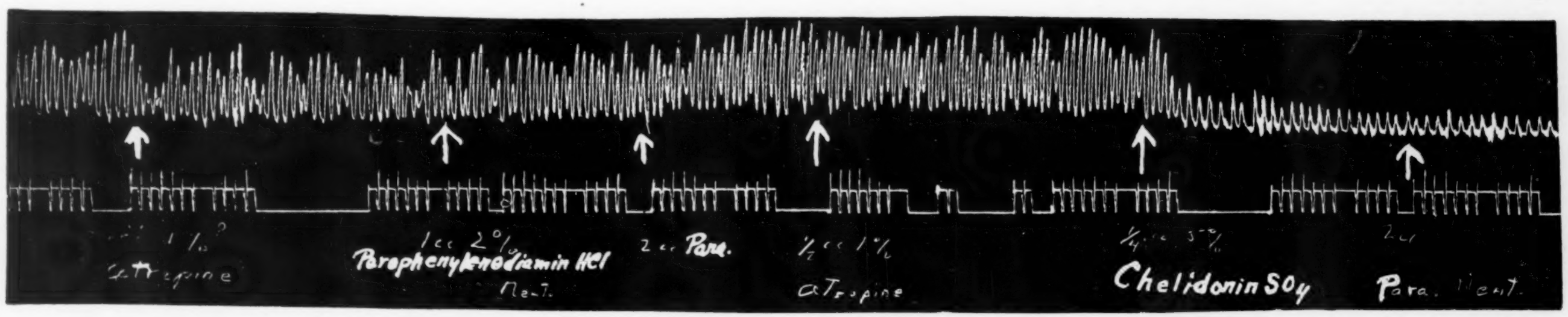



FIG. 8.—Effect of para-phenylenediamine hydrochloride (neutral, 1:8,000) on longitudinal strip of rabbit's intestine previously treated with atropine. Shows increase in tonus and amplitude of contractions, unaffected by treatment with atropine, relieved by chelidonine. Para-phenylenediamine ineffective after muscular depression by chelidonine. Time required for each stroke=five seconds.

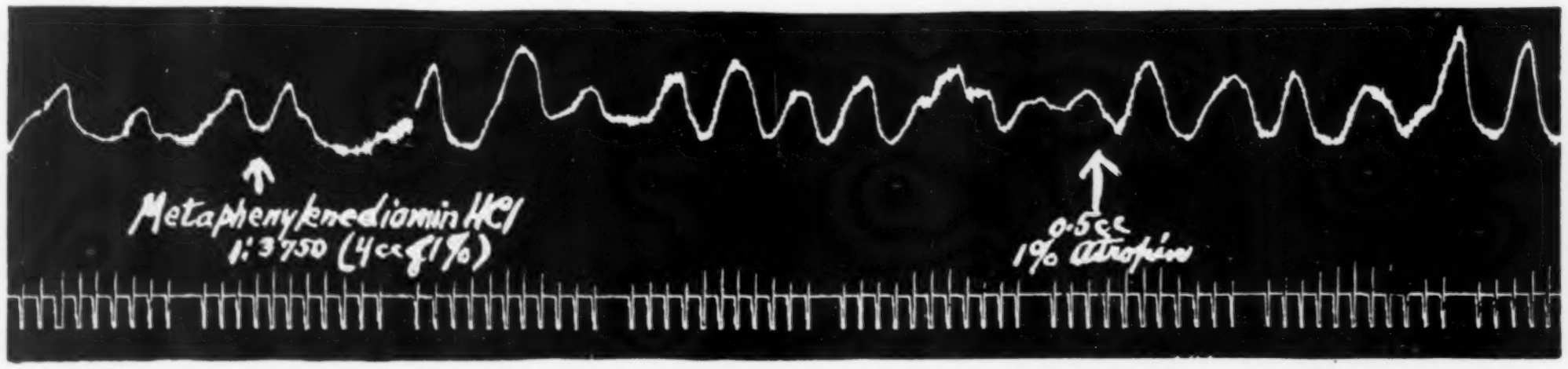



FIG. 9.—Effect of meta-phenylenediamine hydrochloride (1:3,750) on pregnant uterus of rabbit. Shows slight increase in tonus and some increase in amplitude of contractions; unaffected by atropine. Time required for each stroke = five seconds.

artery by the phenylenediamines consists of direct stimulation of smooth muscle independently of nerve connections. This agrees with the stimulant action on cardiac musculature discussed in a previous section.

The effects on the pupil correspond to the very late and toxic actions on excised organs, that is, depression. These may now be described.

*Pupil.*—Enucleated frog's eyes and intact rabbit's eyes were used. Briefly summarized, the dimethyl and diethyl derivatives of para-phenylenediamine in 1 per cent. concentrations caused moderate relaxation of the pupils and rather marked corneal opacities in the majority of eight enucleated eyes. Irrigation with a solution of fluorescein showed permanent staining, indicating injury to the cornea. The dilated pupils of enucleated eyes were sluggishly responsive to light and unaffected by immersion into 1 per cent. solutions of pilocarpine, physostigmine, and barium chloride (also 10 per cent. barium solution), while the controls responded by constriction in the usual way. The pupils of two rabbits were only moderately relaxed, that is, from about 5.5 mm. (original diameter) to about 6.5 mm. (one-half hour after dimethyl-para-phenylenediamine had been applied). This effect was not antagonized by physostigmine. Conjunctivitis and corneal opacities were present from both compounds. These effects were interpreted as inflammatory injury to the eye, with moderate depression of the iris musculature. Similar pupillary and conjunctival changes were not seen in injected animals, until the convulsant stage when dilatation occurred from the asphyxia. Meta-phenylenediamine and para-phenylenediamine produced no noteworthy effects. Since the pupillary changes were rather inconstant and insignificant, the study was not pursued further. Troell* found the effects of para-phenylenediamine on the pupil of different species (dog, cat, rabbit, and guinea-pig) to be variable. Pupillodilatation was not always obtained, and it was uninfluenced by section of the cervical sympathetic ganglion and previous removal of the cervical ganglion. The exophthalmos and orbital edema also persisted after section of the sympathetic ganglion.

*Bronchi.*—A knowledge of the bronchial effects is of importance in explaining the wheezing and asthmatic respiration of animals injected with para-phenylenediamine, and the asthma of workers with fur dyes. It was indicated earlier in the paper that the dyspnea of animals with edema of the neck and face from para-phenylenediamine was due, in part, to swelling of the tongue and of the pharynx. There was probably also a bronchial element, since bronchoconstriction occurred after the injection of dimethyl-para-phenylenediamine and para-phenylenediamine. This was shown in five decerebrate dogs and seven intact guinea-pigs.

In the dogs, which were previously morphinized and decerebrated, changes in bronchial tone were registered from a Meltzer pleural cannula joined by rubber tubing to a tambour, which recorded the excursions on a slowly moving kymograph. Artificial respiration was used to produce the excursions which were reduced during bronchial constriction and increased as a result of relaxation. Figures 10 and 11 illustrate the effects of para-phenylenediamine and dimethyl-para-phenylenediamine on dog's bronchi.

*Troell, A.: Some Attempts to Produce Exophthalmos Experimentally. Arch. Int. Med., 1916, *17*, 382.

The intravenous injection of dimethyl-para-phenylenediamine and para-phenylenediamine was found to give definite bronchoconstriction, and this was promptly relieved by epinephrine and atropine. The doses which gave unmistakable effects—namely, 0.03 gm. per kilo of para-phenylenediamine and 0.0011 gm. per kilo of its dimethyl derivative—usually killed the animals. Smaller doses gave less pronounced effects. Meta-phenylenediamine in the dosage of 0.05 gm. per kilo injected intravenously produced no definite effects on intact bronchi.

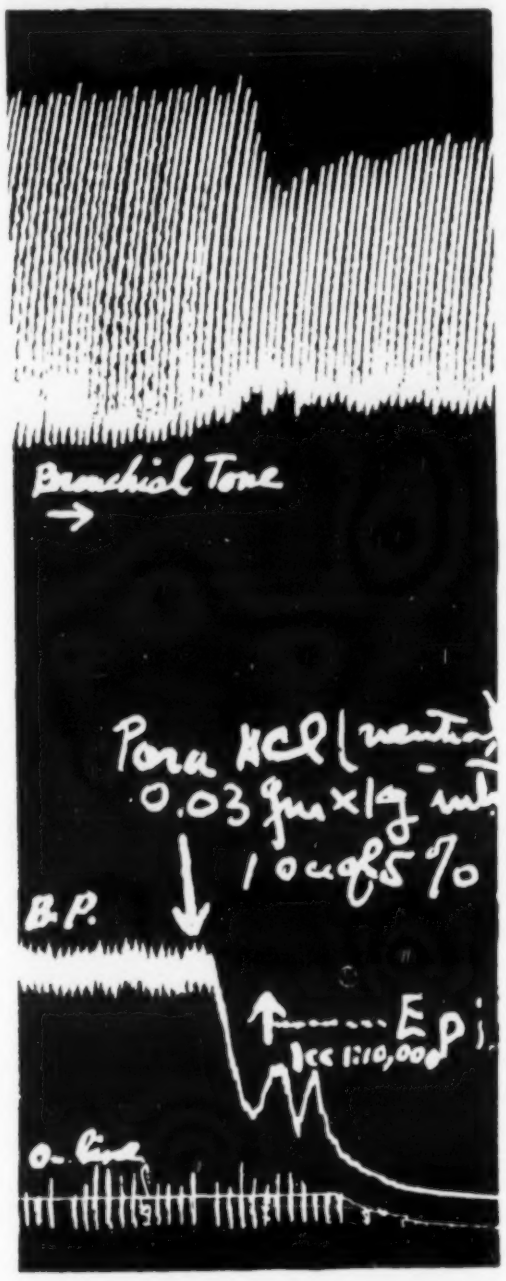



FIG. 10.—Effect of para-phenylenediamine hydrochloride (neutral; 0.03 gm. per kilo intravenously) on bronchi of decerebrated dog (17.5 kg.). Constriction relieved by epinephrine intravenously. Time required for each stroke = five seconds.

The effects of intravenous injection of 0.05 to 0.5 gm. per kilo of dimethyl-para-phenylenediamine into three guinea-pigs consisted of marked increase in respiratory rate, dyspnea, restlessness, gasping, and convulsions; at the end of about ten minutes, there was a marked

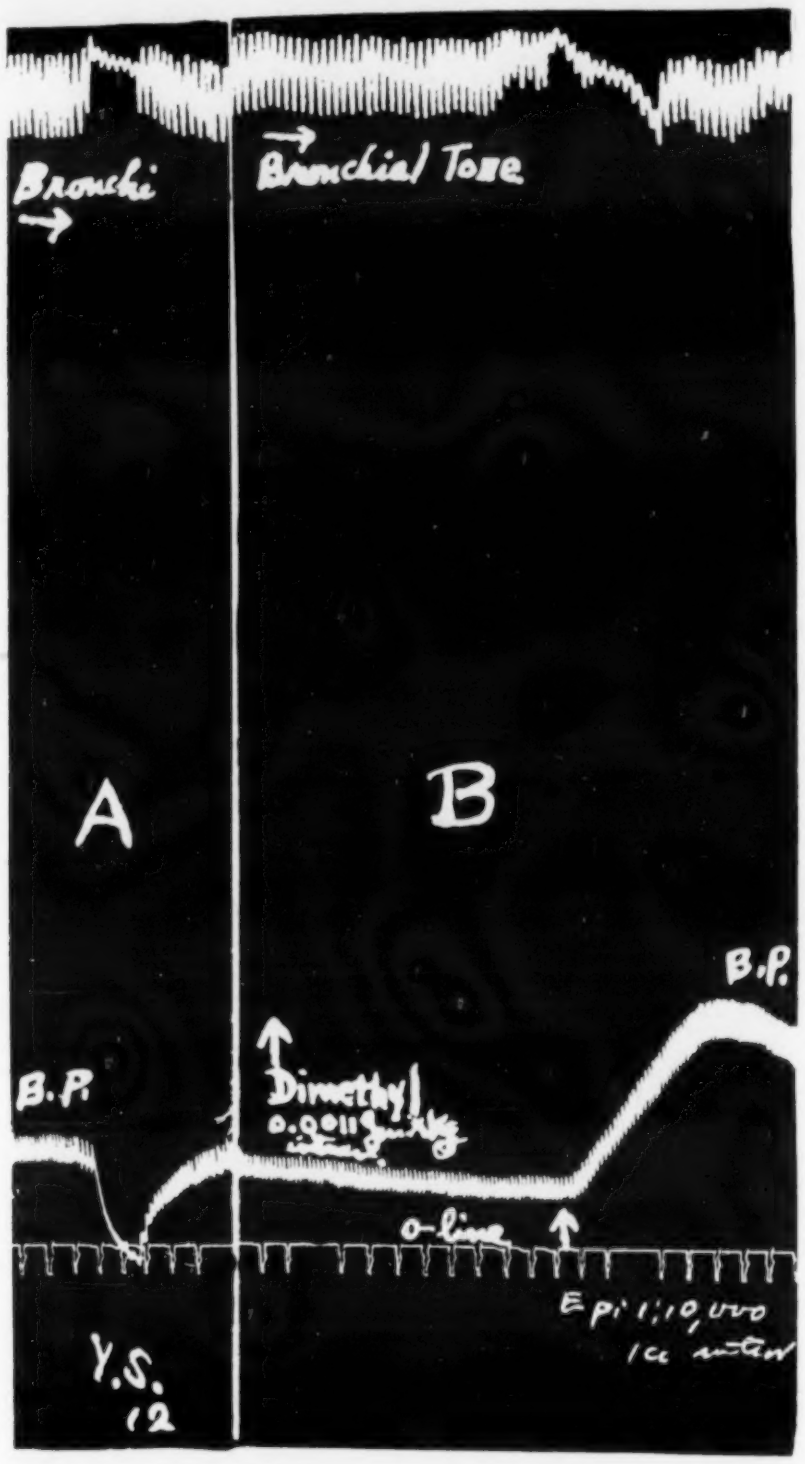



FIG. 11.—Effect of dimethyl-para-phenylenediamine (base, 0.0011 gm. per kilo intravenously) on bronchi of decerebrated dog (4.4 kg.). (A) Bronchoconstriction from stimulation of peripheral ends of both vagi with Harvard inductorium at 12 cm. (B) Bronchoconstriction from 0.0011 gm. per kilo of dimethyl-para-phenylenediamine independently of marked change in blood pressure, relieved by epinephrine (1 c.c. of 1:10,000 intravenously). Time required for each stroke = five seconds.

motor depression and the animals lay on their sides. At the end of fifteen minutes the animals were dead, the respiration having stopped before the heart. At autopsy the lungs were found to be congested, hemorrhagic, and definitely distended, and they floated on

ether; these findings indicated that the lungs contained air from bronchoconstriction as in true anaphylactic shock and from certain anaphylactoid poisons demonstrated in previous studies. The hearts were not dilated.

The results with para-phenylenediamine and meta-phenylenediamine on guinea-pigs were not so well defined as those with dimethyl-para-phenylenediamine, although the majority of the animals used showed evidences of bronchoconstriction. Two guinea-pigs were injected intravenously with 0.042 gm. and 0.26 gm. per kilo of para-phenylenediamine hydrochloride, respectively. Anaphylactoid symptoms were indicated in both animals by restlessness, shivering, jerky movements, increased respiratory rate, and dyspnea. At the end of half an hour both animals were killed. At autopsy, the lungs of the animal which received 0.042 gm. per kilo were pale and partially distended and floated on ether, while the lungs of the animal which received 0.26 gm. per kilo were collapsed, and sank in ether. The two guinea-pigs which were injected with meta-phenylenediamine hydrochloride (0.11 gm. and 0.3 gm. per kilo, respectively) showed moderate anaphylactoid symptoms, consisting of moderate dyspnea and some increase in respiratory rate. The effects were not fatal and the animals were killed at the end of half an hour. At autopsy the lungs of both animals were distended, hemorrhagic, and lighter than ether. From the results of injection experiments, together with the results of experiments on guinea-pigs, it appears justifiable to conclude that the phenylenediamines studied cause constriction of bronchi, and that the effects are most marked with dimethyl-para-phenylenediamine and least marked with meta-phenylenediamine.

### 9. *Skeletal Muscle*

Thus far it has been seen that the phenylenediamines are powerful stimulants of smooth and cardiac muscles. In order to make the study more complete, observations were made on the skeletal muscle of frogs. Two sets of experiments were made. In one set, the phenylenediamines (in the form of hydrochlorides and of bases) were applied directly to frog's gastrocnemius muscle in Ringer's solution, and the contractions were recorded on a slowly moving kymograph. The results consisted of an increase in tonus, with concentrations of 1:10,000, and depression by further addition of solutions of 1:1,000 strength. In the other set of experiments, frog's gastrocnemii were stimulated with minimal break stimuli before and after immersion of the muscles in solutions of different strengths. The results invariably showed an increase in contractility with solutions of 1:10,000 of the different phenylenediamines, and depression with higher concentrations (1 per cent.). These results agree, therefore, with the actions on other muscles.

### 10. *Excretion*

This was observed in animals and in three human subjects. The gastric and hypodermic administration of para-phenylenediamine to rabbits, and of dimethyl-para-phenylenediamine to rabbits and dogs caused marked discoloration of the urine. The urines appeared dark brown and their color was intensified by the addition of hydrogen peroxide and ferric chloride. This means that these compounds were excreted as such in part, and that the darkening of the urine as a result of the addition of oxidizing agents was due to quinonedi-

imine. Whether or not quinonediimine was formed in the body is not definitely known, although its presence in urine was suggested by the dark color. Erdmann and Vahlen laid stress on this point, believing that the formation of quinonediimine in the body was responsible for the irritation and edemas produced by these compounds when administered systemically.

Subjects W. C., P. J. H., and D. each took 0.5 gm. of meta-phenylenediamine hydrochloride (lentin) by mouth and collected urinary specimens at the end of fifteen minutes, one hour, four hours, and twelve hours. Griess' meta-phenylenediamine-nitrite reaction was applied to the urines. This was done by rendering 20 c.c. of urine alkaline with 5 per cent. ammonium hydroxide; then the mixtures were warmed and acidified with 10 per cent. sulphuric acid, and a few drops of 1 per cent. sodium nitrite were added. The presence of meta-phenylenediamine was indicated by the development of an intense yellowish brown to deep brown (Bismarck brown) color. When the test was applied in this way to all urines, only the four-hour and twelve-hour specimens in two of the subjects (W. C. and P. J. H.) gave unmistakable brownish colorations, indicating the presence of meta-phenylenediamine. The fact that both of these specimens were darker in color than the fifteen-minute and one-hour specimens of these subjects indicated the presence in the urines of the oxidation product, quinonediimine. The urines of subject D. were light in color and gave negative results with Griess' reaction. Apparently the meta-phenylenediamine was not absorbed, or else the urines were too dilute. None of the subjects experienced any symptoms after taking the drug. Under the name of lentin, meta-phenylenediamine has been advocated as an antidiarrheal remedy. When the facts, namely, that it increases the peristalsis of excised intestine, that it is not astringent, and that it is absorbed to some extent (as indicated by its excretion), are considered, it is difficult to understand the basis for its alleged antidiarrheal action.

## V. Discussion

The results of this study indicate that the phenylenediamines are definitely toxic compounds. Dimethyl-para-phenylenediamine was found to be the most toxic, and meta-phenylenediamine probably the least toxic, although in some animals it appeared to be about as toxic as para-phenylenediamine. Diethyl-para-phenylenediamine is about as toxic as the para compound. A summary of the principal actions of the phenylenediamines studied is presented in Table 2, and requires no further discussion. The rapid development of symptoms of toxicity after dermal application is a unique feature among the actions of dimethyl-para-phenylenediamine and diethyl-para-phenylenediamine, the fatal dosage from skin being practically no greater than that by hypodermic administration. This indicates unusual rapidity of absorption and is connected with the marked volatility and lipoid solubility of these bases. On the assumption that the absorption from human skin is about the same as that from rabbit's skin, it is estimated that about a teaspoonful of dimethyl-para-phenylenediamine held on the palm of the hand would constitute a fatal dose for an adult man of 60 kilos body-weight. This is of importance in poisoning from the handling of the compound itself and of articles dyed and treated with it in vari-

ous industries. It means that effects on the higher functions are possible from skin absorption. Barring individual differences, dimethyl-para-phenylenediamine is one of the most efficient skin irritants known, though probably not surpassing dichlorethylsulphide (mustard gas) whose actions it does not modify sufficiently to be of therapeutic importance in the treatment of burns and other lesions. Its toxicity is against its use for this purpose. Furthermore, these compounds, in basic form, are volatile, and their vapors cause death when inhaled by animals. They also act as irritants to the respiratory tract, causing and rendering it susceptible to rhinitis, pharyngitis, bronchitis, and even pneumonia if enough is inhaled.

The salts are non-irritant for skin, and indicate a method of treatment of the lesions produced by the bases. Accordingly, acetic acid, which can be used without injury in fairly high concentrations (10 per cent. and higher), was found to be efficient for prevention of lesions before marked itching occurred.

Under the conditions of the experiments, para-phenylenediamine and meta-phenylenediamine were not sufficiently irritant to the skin of animals and of man to require further discussion. This might be quite different with repeated applications or with applications applied to the injured skin, and in instances of chronic poisoning from the use of para-phenylenediamine in hair dyes and in dyed furs in the fur industry.

All the phenylenediamines produce definite systemic effects after absorption. They stimulate the circulation, respiration, and smooth muscle of excised organs, and cause bronchoconstriction. Asthma and local inflammations of the respiratory tract among workers in the fur dyeing industry are commonly reported. The claim that sensitization from articles dyed or treated with phenylenediamine and its oxidation product will explain the symptomatology on the basis of anaphylaxis, was found to be untenable. The phenylenediamines, and presumably also quinonediimine, irritate directly through their inherent chemical properties and do not act through other mechanisms. The local irritation occurs independently of precipitation in the tissues. It is more probable that direct bronchial stimulation and irritation by para-phenylenediamine, rather than anaphylaxis, are the cause of the asthma of fur dyers. Disturbances of the circulation and alimentary tract from the phenylenediamines under industrial conditions are also conceivable. Workmen should, therefore, be protected against these compounds in industry, and the use of para-phenylenediamine in hair dyes and other cosmetics should be prohibited.

The production of facial and cervical edemas by para-phenylenediamine, and of hydrothorax and possibly hydroperitoneum by meta-phenylenediamine is of interest mainly to experimental pathology and pharmacology. Facial and cervical edemas in human individuals have been reported in poisoning from the use of hair dyes containing para-phenylenediamine.

Therapeutically, the phenylenediamines are of no significance. A scientific basis for the alleged antidiarrheal and antidysenteric properties of meta-phenylenediamine (lentin) is lacking, and its use is unwarranted. Experimental evidence indicates that it would increase peristalsis, if anything, and that it might be harmful otherwise (by the production of effusions).

## VI. Conclusions

1. The phenylenediamines, which are used extensively in industry, arts, and science, are definitely toxic compounds and possess a variety of striking pharmacological actions.

TABLE 2.—SUMMARY OF IMPORTANT ACTIONS OF SOME PHENYLENEDIAMINES

| Compounds Studied (Arranged in Descending Order of Toxicity) | Skin Irritation and Vesication | Circulation | Respiration | Temperature | Smooth Muscle of Excised Organs[1] | Convulsant Action | Production of Systemic Edema and Exudates | Vapor Toxicity |
|---|---|---|---|---|---|---|---|---|
| Dimethyl-para-phenylenediamine | positive | marked stimulation[2] | marked stimulation | lowered | fleeting depression followed by marked stimulation (chiefly tonus) | positive | negative | positive |
| Diethyl-para-phenylenediamine | " | less marked stimulation | the same | " | the same | " | " | negative |
| Para-phenylenediamine | negative | moderate stimulation | moderate stimulation | " | moderate stimulation (chiefly amplitude) | " (less pronounced) | positive as to edemas | " |
| Meta-phenylenediamine | " | the same | the same | " | the same | " (least pronounced) | positive as to exudates | " |

[1] Intestine, uterus, bladder, stomach, ureter, aorta, pupil (also intact pupil) and intact bronchi.

[2] Increase in pulse rate, rise in blood pressure, systolic tendency of heart and increase in kidney volume. Increased rate and systolic tendency of excised turtle heart and increased tone of dog's ventricle (strips).

2. According to the minimal fatal dosage in several species, the compounds that were studied arrange themselves in descending order of toxicity as follows: dimethyl-para-phenylenediamine, diethyl-para-phenylenediamine, para-phenylenediamine, and meta-phenylenediamine.

3. Because of their volatility and marked lipoid solubility, dimethyl-para-phenylenediamine and diethyl-para-phenylenediamine, in basic form, are absorbed from the unbroken skin of rabbits, and cause systemic symptoms of poisoning and death. The vapors of dimethyl-para-phenylenediamine are toxic to animals.

4. Locally, dimethyl-para-phenylenediamine and diethyl-para-phenylenediamine, in basic form, are marked irritants, and cause dermatitis with marked edema of the skin of rabbits and dogs, and dermatitis and vesication on human skin. Their salts are non-irritant. Treatment of skin with acetic acid before

itching develops prevents the burns. Meta-phenylenediamine and para-phenylenediamine are very slightly, or not at all, irritant in acute experiments, but the result might be different with repeated applications or with applications on broken skin. Gastric administration causes nausea and vomiting in cats and dogs.

5. Systemically, all the phenylenediamines cause definite symptoms—namely, stimulation of the circulation and respiration, fall of body temperature, tremors, increased reflex excitability, convulsions, coma, and death.

6. Intravenously, the circulatory effects are characterized by initial fleeting depression, followed by marked stimulation of cardiac musculature with corresponding changes in pulse rate, cardiac volume, blood pressure, and kidney volume.

7. The convulsions in mammals are due to the compounds themselves. In frogs, a narcotic or morphine-like action occurs.

8. Besides these changes, the hypodermic and gastric administrations of para-phenylenediamine produce in rabbits a peculiar, specific edema of the face, nose, tongue, conjunctiva, and neck, while meta-phenylenediamine causes hydrothorax, and possibly hydroperitoneum. The dosage necessary to produce this effect, and the response of rabbits are variable. White rats failed to respond with edema and exudate formation to the meta and para compounds; and rabbits, white rats, cats, and dogs failed to respond to dimethyl-para-phenylenediamine and diethyl-para-phenylenediamine, because of the marked toxicity of these compounds.

9. The production of edemas and exudates by these compounds is of interest to experimental pathology and pharmacology. The mechanism by which these lesions are produced remains unsolved.[1]

10. The principal action of the phenylenediamines on smooth muscle of excised organs (intestine, stomach, esophagus, uterus, ureter, bladder, aorta, and renal artery) consists of stimulation independently of nerve connections, and is most pronounced (especially tonus) with dimethyl-para-phenylenediamine and least pronounced with meta-phenylenediamine. The pupils of enucleated and intact eyes are dilated, and intact bronchi are constricted.

11. The asthma and respiratory symptoms of workers in the fur-dye industry, in which para-phenylenediamine is used, are due, therefore, to direct irritation and bronchial stimulation rather than to anaphylaxis.

12. The results of this investigation indicate that workmen should be protected against the phenylenediamines used in various industries, and that the use of para-phenylenediamine in hair dyes and cosmetics should be prohibited.

13. Therapeutically, the phenylenediamines are of no importance, and a scientific basis for the alleged benefits of meta-phenylenediamine (lentin) as an antidiarrheal and antidysenteric remedy is lacking.

[1] While this paper was in galley proof, a paper entitled, "The Edema of Paraphenylenediamin," by O. S. Gibbs, appeared in the *Journal of Pharmacology and Experimental Therapeutics*, 1922, *20*, 221. Gibbs leaves the mechanism of the edema (in cats) unsolved, although he suggests changes in blood colloids as being fundamentally concerned. His evidences for this are not convincing.